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WJC 6th Anniversary Special Issues (1): Hypertension

African Americans, hypertension and the renin angiotensin system

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Abstract

African Americans have exceptionally high rates of hypertension and hypertension related complications. It is commonly reported that the blood pressure lowering efficacy of renin angiotensin system (RAS) inhibitors is attenuated in African Americans due to a greater likelihood of having a low renin profile. Therefore these agents are often not recommended as initial therapy in African Americans with hypertension. However, the high prevalence of comorbid conditions, such as diabe-

tes, cardiovascular and chronic kidney disease makes treatment with RAS inhibitors more compelling. Despite lower circulating renin levels and a less significant fall in blood pressure in response to RAS inhibitors in African Americans, numerous clinical trials support the efficacy of RAS inhibitors to improve clinical outcomes in this population, especially in those with hypertension and risk factors for cardiovascular and related diseases. Here, we discuss the rationale of RAS blockade as part of a comprehensive approach to attenuate the high rates of premature morbidity and mortality associated with hypertension among African Americans.

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Key words: African American; Blood pressure; Ethnicity; Hypertension; Renin; Angiotensin

Core tip: African Americans have exceptionally high rates of hypertension and hypertension related complications. Due to a greater likelihood of having a low plasma renin levels, inhibitors of the renin angiotensin system (RAS) are often not recommended as initial antihypertensive therapy. However, animal models suggest hypertension characterized by low circulating renin levels have a paradoxical increase in tissue RAS activity. Thus treatment with RAS inhibitors may be critical to preventing end organ damage. We describe the rationale of RAS blockade as part of a comprehensive approach to attenuate the high rates of premature morbidity and mortality associated with hypertension among African Americans.

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INTRODUCTION

Hypertension is characterized by a persistent and frequently progressive elevation in blood pressure^[1]. The level of systolic blood pressure (SBP) and/or diastolic blood pressure (DBP), which connotes a diagnosis of hypertension, may vary depending on the presence or absence of coexisting comorbidities^[1,2]. Hypertension is commonly defined as physician diagnosed SBP ≥ 140 mmHg and DBP ≥ 90 mmHg; and pre-hypertension is defined as SBP ≥ 120 mmHg and < 140 mmHg or DBP ≥ 80 mmHg and < 90 mmHg^[1]. However, a recent report from the panel members appointed to the Eighth Joint National Committee recommended a SBP goal of < 150 mmHg and DBP goal < 90 mmHg in persons ≥ 60 years of age without diabetes mellitus (DM) or chronic kidney disease (CKD)^[3]. The committee also recommended that in the African American hypertensive population, including those with diabetes, initial therapy should begin with a calcium channel blocker or thiazide-type diuretic, but acknowledged that there was modest evidence for renin-angiotensin system (RAS) inhibition as initial or add-on antihypertensive therapy in African Americans with CKD^[3]. However, a minority of the committee members did not support a higher SBP goal at age ≥ 60 years or the choices for initial antihypertensive therapy in African Americans. They were particularly concerned that the newly recommended higher blood pressure goal may adversely affect patients aged ≥ 60 years with cardiovascular disease (CVD) risk factors other than DM or CKD^[4]. In addition, they interpreted the evidence supporting an increase in the SBP target from < 140 mmHg to < 150 mmHg in persons 60 years of age or older as insufficient and inconsistent with the evidence supporting the panel's recommendations for an SBP target of < 140 mmHg in younger persons^[4]. There is also the risk that as the new guidelines are disseminated that the "take home" messages may miss the nuances such as the new recommended higher goal in persons ≥ 60 years of age excluding persons with DM or CKD, and that with a goal of < 150 mmHg many patients may spend much of their time with their blood pressure (BP) above that level.

In the United States African Americans develop hypertension at an earlier age than whites, have much higher average blood pressure readings, a greater likelihood of refractory hypertension, and greater rates of premature hypertensive complications such as CKD, stroke and heart disease^[5-7]. Importantly, African Americans suffer from a three-fold higher death rate from hypertension with cardiovascular complications accounting for the majority of deaths^[5]. Data from the National Health and Nutrition Examination Survey (NHANES) indicate/show that although there has been a trend toward improving BP control among African Americans, the overall control of BP remains suboptimal at a national level. During the period from 1999-2004, blood pressure was adequately controlled in only 35% of whites, 29% of African Americans, and 27% of Hispanics^[8]. By 2007-2008

blood pressure control rates had increased to 50% and for the first time were now similar across race/ethnicity^[9]. While this is a marked improvement, it still represents half of Americans with hypertension having poor blood pressure control. However other data underscore the lingering concern for BP control as a significant problem among African Americans. In the Multi-Ethnic Study of Atherosclerosis (MESA) the percentage of treated but uncontrolled hypertension was significantly higher in African Americans (35%), Chinese (33%), and Hispanics (32%) than in whites (24%)^[10]. After adjustment for clinical and socioeconomic factors the relative higher rates of uncontrolled hypertension for Chinese and Hispanic participants largely disappeared, but persisted in the African American population, suggesting an independent effect to account for these observed differences such as other biologic and/or non-biologic factors not assessed in the MESA study^[10].

BIOLOGIC FACTORS INFLUENCING HYPERTENSION IN AFRICAN AMERICANS

The reasons for the exceptionally high rates of hypertension and associated end organ damage among African Americans, are not entirely clear but likely include socioeconomic status, lifestyle choices, clinical factors (*e.g.*, increased risks of diabetes and hypertension), environmental, and biologic/genetic factors that may contribute broadly to racial/ethnic differences in not only outcomes but in response to therapeutic intervention^[11-17]. Our understanding of the complex factors that predispose African Americans to hypertension and hypertension-related complications is evolving. While RAS inhibition has emerged as an important antihypertensive therapy, the blood pressure lowering efficacy of RAS inhibitors is attenuated in African Americans^[18], likely due to an increased prevalence of having a low renin profile. Therefore these agents may be less likely to be recommended as initial therapy in African Americans with hypertension^[3].

One major biologic factor that is highly relevant to RAS inhibition is the particularly high prevalence of salt sensitivity in African Americans, which is also associated with a low circulating plasma renin profile^[19-26]. Salt sensitivity is defined as an increase in blood pressure in response to sodium or salt intake, and is commonly associated with a low circulating renin profile^[24,27,28]. Wilson *et al.*^[29] postulated that the slave trade from Africa to the Americas led to extreme volume depletion and cardiovascular collapse during the journey due to diarrheal diseases and limited access to water favoring the survival of persons who were avid sodium retainers and accelerating gene selection for sodium retention. Consistent with this premise, Maseko *et al.*^[30] found no relationship between blood pressure and 24-h urinary sodium and potassium excretion rates in nearly 300 city-dwelling black South Africans, suggesting African slave descendants have a

higher rate of salt sensitivity than native black Africans. However many of the historical claims which form the basis of the slavery hypothesis for hypertension have been challenged by other authors^[29,31]. In question are the key tenets of the theory which implicate salt deficiency in the areas of Africa from which slaves originated, the trauma of the slave trade, and conditions in the Americas as triggers for unnatural genetic selection for renal sodium-retainers^[29,32]. According to this theory, these factors collectively evolved into the eventual present-day disproportionately higher blood pressure in African Americans compared with their counterpart whites or African blacks in modern sodium-rich societies^[29,31,32]. In the absence of access to records of past salt availability in Africa, slave trade disease states, and dietary salt content in the Americas between the 16th and 19th century, it will be impossible to ever fully confirm or fully refute this hypothesis^[33]. However, others have refuted the slave trade hypothesis as contributing to excess rates of hypertension in blacks of African descent^[31].

Some specific features of salt-sensitive hypertension have been characterized. Evidence suggests that the sympathetic nervous system may play a role in the modulation of salt sensitivity. In the presence of salt loading, the typical response of the sympathetic nervous system is to decrease norepinephrine, a known sodium retainer, and to increase dopamine which promotes sodium excretion^[34,35]. However in salt sensitive hypertensive individuals, particularly African Americans, there appears to be a dysfunctional response of the sympathetic nervous system in the presence of excess salt. In these patients, salt loading is associated with decreased urinary dopamine levels and the absence of any significant decreases in norepinephrine^[35,36]. Another factor which is implicated as accounting for differences in salt sensitivity is kallikrein which has been demonstrated to be excreted in lower levels in salt sensitive hypertensive persons, particularly African Americans^[37,38]. Whether the fact that African Americans consume less potassium, a known kallikrein releaser, is contributory, remains unclear^[24,37]. Evaluation of the relationship between potassium intake, urinary kallikrein levels and salt sensitivity is warranted using large scale clinical trials.

Among the non-biologic factors which could possibly explain the inequity in the occurrence of hypertension among the races, obesity remains a tempting option given its similar trend of increased prevalence in African Americans. Excess adiposity, a reflection of lifestyle habits, has a reported 51% greater prevalence in this population. In addition, there has been an association reported between obesity, insulin resistance and other adipokine-mediated pathways with the occurrence of salt-sensitivity^[39]. However, NHANES data from the 1988-1994 time period show no significant difference in obesity between white men and black men (20.3% and 21.1% respectively) while there was a 46% greater prevalence of hypertension in black men over white men during that same period^[39]. Also, Okosun *et al*^[40] have shown that the risk of African

American race for high blood pressure remains after adjusting for abdominal adiposity in NHANES III data. Therefore the evidence does not support obesity as the sole contributor to the disparity in prevalence of hypertension among blacks although it is not excluded as a contributory factor.

RENIN-ANGIOTENSIN SYSTEM IN SALT SENSITIVE HYPERTENSION

The disproportionate burden of both hypertension and its sequelae in African Americans underscores the significance of optimizing approaches to blood pressure control in order to prevent and/or attenuate the high rate of hypertensive complications. A comprehensive understanding of the role of RAS blockade as part of a strategy for blood pressure control and attenuation of end organ disease is critical to selecting therapeutic agents which might reverse hypertension related premature morbidity and mortality. The RAS system is an important modulator of blood pressure and vascular function/disease.

As noted above, in addition to an increase in the prevalence of salt sensitivity, an increased prevalence of reduced plasma renin levels have been noted in hypertensive African Americans and Caribbean Hispanics^[41-43]. Given the documented role of RAS in the progression of vascular disease, an attenuated risk of hypertension-related end-organ damage might also be expected in patients with low-renin hypertension. Paradoxically, however, many such individuals experience high rates of hypertension-related end-organ complications suggesting RAS may still be important at the tissue level in patients with reduced plasma renin levels.

Much of our understanding of the role of the RAS in blood-pressure regulation at a tissue level derives from Dahl salt-sensitive and salt-resistant rat studies as a model of human salt-sensitive, low renin hypertension that is more commonly noted in African Americans^[44]. Consumption of a high-salt diet by Dahl salt-sensitive rats results in hypertension and early onset of renal injury and dysfunction. This is associated with reduced plasma renin activity and angiotensinogen (ATG) concentrations, but accompanied by paradoxical elevations of renal tissue angiotensin (Ag) II, tissue Ag II receptor 1 (AT1) receptor expression and urinary ATG excretion as well as oxidative stress and activation of NAD(P)H oxidase in the kidney and cardiovascular tissues^[45,46]. These observations support a dissociation of low circulating RAS from the upregulated intrarenal and tissue RAS in this model. Despite the low circulating renin level, RAS blockade in Dahl salt-sensitive rats fed a high-salt diet reversed endothelial dysfunction, attenuated proteinuria and reduced cardio-renal injury even though it did not normalize the blood pressure supporting a blood pressure independent RAS related effect^[47]. These findings suggest that the intrarenal and tissue RAS may be more important in the pathogenesis of salt sensitive hypertension and hyper-

tensive nephropathy than the circulating RAS, which may be more reflective of the regulation of sodium balance, vascular resistance and arterial blood pressure.

The efficacy of RAS inhibition has also been shown to be widely effective in many other animal models of hypertension, including but not limited to hypertension in obese Zucker rats animals with renal mass reduction^[48,49] and rodents with hypertensive nephropathy induced by Ag II infusion^[50]. Osteopontin (OPN), which is a secreted matrix glycoprotein that is expressed in Ag II-injured tissues, is an important modulator of several of the Ag II-induced mechanisms of hypertensive nephropathy. Global deletion of OPN in hypertensive, albuminuric mice promoted Ag II-induced monocyte chemoattractant protein-1, NADPH oxidase subunits (NOX2, gp47phox and NOX4) and plasminogen activator inhibitor-1, compared to Ag II-infused wild-type mice^[50]. Also, inhibition of OPN expression may account for a mechanism by which Ag II blockade attenuated renal injury following renal ablation^[51], consistent with OPN modulating the effects of Ag I converting enzyme (ACE) inhibitor therapy in hypertensive nephropathy. Finally, Gonzalez-Villalobos *et al.*^[52] recently demonstrated that the absence of kidney ACE substantially blunts the hypertension induced by Ag II infusion or nitric oxide synthesis inhibition. Moreover, in mice that lack kidney ACE the renal responses to high serum Ag II such as intrarenal Ag II accumulation, sodium and water retention, and activation of transporter activating kinases Ste20-related proline alanine-rich kinase and oxidative stress response kinase were effectively prevented. These findings led them to conclude that renal ACE activity is required to increase local Ag II to stimulate sodium transport and induce hypertension^[52]. These findings are consistent with the importance of inhibition of intrarenal RAS to attenuate hypertension and its sequelae.

In summary, hypertension has been reported in animal models to induce glomerular hypertension and glomerular hyperfiltration, oxidative stress, inflammation, endothelial damage due to enhanced traffic of plasma proteins and/or increased translational and shear forces and other that may lead to worsening vascular disease, CKD and worsening blood pressure^[53,54]. Ag II is one of the more extensively studied mediators of vascular function. Ag II upregulates transforming growth factor- β 1, tumor necrosis factor- α , nuclear factor- κ B, OPN, several adhesion molecules and chemoattractants, and more recently, interactions with adiponectin and select microRNAs which together conspire to promote renal inflammation and fibrosis^[55,56]. The documented role of RAS in the progression of end organ damage has positioned it as a prime therapeutic target in high-risk patients. RAS blockade can reduce blood pressure, reverse endothelial dysfunction, attenuate proteinuria, and reduce renal injury independent of blood pressure changes^[47]. The paradoxical increase in tissue RAS in salt sensitive, low renin hypertension makes RAS blockade an important therapeutic option for treating African Americans and other patients

with hypertension and a circulating low renin profile^[44].

GENETIC POLYMORPHISMS, THE RAS, AND HYPERTENSION IN AFRICAN AMERICANS

At the level of the kidney the pool of intra-renal RAS is upregulated in CKD independently of systemic RAS. This pathological upregulation of the intra-renal RAS is marked by simultaneous increases in the AT1 expression and the number of the Ag II-producing cells, many of which are macrophages and serve as ectopic sources of angiotensin^[57]. In addition, the kidney not only contains ATG, angiotensin converting enzyme, and renin, but is a recipient of their physiological and pathophysiological actions^[58,59]. In CKD, AT1 receptor activation by Ag II raises superoxide production *via* upregulation of NAD(P)H oxidase, and inhibits Nrf2 expression, which is the master regulator of genes encoding many antioxidant and cytoprotective enzymes and related molecules^[60-62]. This may be an important mechanism of action through which intra-renal RAS promotes, oxidative stress, inflammation and subsequent tissue damage and dysfunction in animals, and likely humans with CKD and/or hypertension.

Several genetic variations (*e.g.*, promoter region variants of the *ATG* gene) have been identified which may contribute to ethnic disparities in salt-sensitive hypertension and response to RAS blockade. Tiago *et al.*^[63] reported a marked influence of homozygosity for the -20A allele ($n = 399$) of the ATG on the relationship between body mass index and systolic blood pressure ($r = 0.23$; $P < 0.0001$) in over 1000 South Africans of African ancestry. More specific to the response to RAS inhibition, the African-American Study of Kidney Disease and Hypertension (AASK) study showed that African Americans who were homozygous for the ACE polymorphism 12269G > A experienced a more rapid reduction in blood pressure following ACE inhibition than those who were heterozygous for this variant ($P < 0.001$), but blood pressure response to calcium channel blockers did not vary by ACE polymorphism variants^[64]. Similarly, ATG promoter region variants among a cohort of South Africans of African ancestry influenced the blood pressure response to an Angiotensin converting enzyme inhibitor (ACEI), but not to a calcium channel blocker^[65]. Recent genome-wide admixture mapping studies have demonstrated genetic variation in the regions of MYH9 and APOL 1 on chromosome 22 that have been estimated to explain over 50% of the difference in the rates of non-diabetic end-stage renal disease (ESRD) between white and black Americans^[13,66-69], but to date no reports have linked these gene variants to response to RAS inhibition therapy. Limited data exist for the study of ACE polymorphism variants in animal models of high BP. One report suggested a locus for the inducible, but not a constitutive, nitric oxide synthase cosegregated with

blood pressure in the Dahl salt-sensitive rat^[70], while microsatellite of ACE was reported to be associated with the development of salt-sensitive hypertension in the stroke-prone spontaneously hypertensive rat^[71].

TREATMENT TRIALS OF RAS INHIBITION IN AFRICAN AMERICANS

Most clinical trials of RAS inhibition as primary antihypertensive therapy in African Americans have been directed toward patients with diabetes, CKD, and/or high CVD risk. A summary of select trials of RAS inhibition as primary antihypertensive therapy in African Americans follows.

Diabetes

The Collaborative Study Group was the first major study to examine the efficacy of ACEI in slowing the progression of CKD in 409 participants with type 1 diabetes^[72], and while it demonstrated efficacy in comparison to usual care, the study included only 15 African Americans. Two subsequent major studies of RAS inhibition in persons with diabetic nephropathy, most of whom had hypertension, were the irbesartan (IDNT) and losartan (RENAAL) trials. These two trials both showed efficacy for ARB therapy and included higher proportions of ethnic minorities than most earlier studies with 13% African Americans and 5% Hispanics in the former and 15% African Americans and 18% Hispanics in the latter^[73,74]. Although not powered to perform subgroup analyses according to ethnicity, these studies strongly suggest that the positive outcomes of RAS inhibition extended to all study participants. Moreover, a post-hoc analysis of RENAAL found no ethnic differences in the relationship of baseline albuminuria or 6-mo antiproteinuric response to therapy to ESRD risk, or the overall renoprotective effect of ARB therapy (1513 participants followed for 3.4 years with final SBP of 141 mmHg)^[75].

CKD

The AASK is the largest prospective CKD study to focus on African Americans to date^[76,77]. The AASK trial ($n = 1094$) was a randomized controlled study that examined the effects of three classes of initial antihypertensive therapy (ACEI, β -blocker or calcium channel blocker) and two levels of blood pressure control: intensive ($\leq 120/80$ mmHg) and standard (approximately 135-140/85-90 mmHg) on the progression of renal function and clinical outcomes in a high-risk cohort with hypertension-related CKD^[78]. Diuretics were not among the three randomized classes of antihypertensive agents as it was assumed the majority of study participants would require diuretic therapy due to their impaired renal function and associated volume retention and therefore the majority of study participants would require diuretics, allowing the design to most closely emulate clinical practice. Indeed, nearly 90% of AASK participants re-

quired adjunct diuretic therapy to achieve target blood pressure levels. While calcium channel blockers were the most commonly prescribed antihypertensive for African Americans with CKD due to their blood pressure lowering efficacy, the calcium channel blocker arm of AASK was terminated early because of increased rates of adverse clinical events^[76]. AASK demonstrated that clinical cardio-renal outcomes in African Americans: were improved with ACEI in comparison to β -blocker or calcium channel blocker, with diuretics and other agents added as needed^[79]. While outcomes did not initially differ between intensive ($\leq 120/80$ mmHg) and standard (approximately 135-140/85-90 mmHg) BP targets^[79], longer term follow up (8.8 to 12.2 years) in the intensive control group (mean blood pressure was 130/78 mmHg) compared to standard care (141/86 mmHg) revealed a benefit in patients with baseline protein-to-creatinine ratio > 0.22 (equivalent to baseline protein excretion of > 300 mg/d), but not the overall cohort^[80].

Importantly, AASK demonstrated that blood pressure can be controlled in African Americans with CKD and that combined clinical outcomes (cardiovascular and renal) can be improved by using not only a beta blocker or calcium channel blocker but an ACEI as initial therapy to reach a usual or strict blood-pressure target, with diuretics in most, and other agents added as needed^[71], and that ACEI therapy led to the best clinical outcomes^[79]. This contrasts previous^[7] and more recent suggestions^[3] that RAS inhibition is of limited benefit in African Americans. The notion of the overall efficacy of RAS inhibition is further supported by a recent meta-analysis of 25 randomized controlled trials ($n = 45758$) by Balamuthusamy *et al*^[81] who found improved or equivalent CVD outcomes in patients with diabetic or non-diabetic CKD and proteinuria treated with RAS blockade (ACEI/ARB) in comparison to placebo and control (β -blocker, calcium-channel blockers and other antihypertensive-based therapy). While the ethnic composition of the meta-analysis was not provided, the preponderance of evidence supports the important role for RAS blockade in treating patients with CKD and proteinuria, including African Americans. Secondary analysis of Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) trial, detailed below, showed that in patients with reduced renal function, RAS inhibition with lisinopril was equally as effective as amlodipine and chlorthalidone in reducing the rate of development of ESRD^[82].

HIGH CARDIOVASCULAR RISK

The Heart Outcomes Prevention Evaluation trial assessed the effectiveness of RAS inhibition in nearly 10000 high-risk patients (55 years of age or older) who had evidence of vascular disease or diabetes plus one other cardiovascular risk factor, but no evidence of over health failure^[83]. They found ramipril significantly reduced the rates of death, myocardial infarction, and stroke^[83]. Unfortunately, the racial/ethnic composition of the study cohort was

not described. Another key hypertension trial, which included ACEI therapy and a large percentage of minority participants, was the ALLHAT. ALLHAT enrolled nearly 34000 high-risk hypertensive patients, of whom 32% were black and 16% were Hispanic^[84]. ALLHAT analysis found that first-line therapy with chlorthalidone, amlodipine or lisinopril were similar in efficacy for preventing cardiovascular events^[85]. First-line therapy with alpha blockade was not as effective and the alpha blocker arm was discontinued early^[86]. Subgroup analysis by race/ethnicity revealed no significant differences by class of therapy from that of the overall trial results. Unfortunately the second line drug for both amlodipine and lisinopril could not be a diuretic or a complementary RAS inhibitor or calcium channel blocker, respectively, so the design limited the ability of ALLHAT to test common clinical practice and practice guidelines. This is especially important for African Americans with high blood pressure who are more likely to require 2 or 3 drugs to achieve blood pressure goal and especially important for RAS inhibition which has been most effective in combination with a diuretic when a second agent is needed^[79]. Many authorities still favor initial therapy with RAS blockade, especially in patients with hypertension complicated by diabetes, CKD, or CVD where diuretics are commonly included in treatment^[1,2,87]. Secondary analysis of ALLHAT showed that in patients with reduced renal function, RAS inhibition with lisinopril was equally as effective as amlodipine and chlorthalidone in reducing the rate of development of ESRD^[82].

SPECIAL CONSIDERATIONS FOR THE USE OF ACEI IN TREATING HYPERTENSION IN AFRICAN AMERICANS

Consideration is necessary of the well-recognized common effects noted with some agents that inhibit the RAS system. ACEI related adverse events are relatively common in African Americans and Chinese^[88-90]. Of note, the rate of angioedema in blacks is three times that of non-blacks^[88,89], and the rate of ACEI discontinuation due to cough is also very high^[91]. Possible mechanisms which could account for the increased incidence of ACEI-related adverse effects in African Americans are angiotensin-converting enzyme and bradykinin gene polymorphisms as have been demonstrated in East Asians^[92]. Also notable is that the initiation of RAS inhibition therapy can lead to an acute reduction in renal function regardless of racial/ethnic background, especially in patients with advanced CKD. In most instances this reduction in glomerular filtration rate is a potentially reversible physiologic hemodynamic effect and a modest initial fall in renal function may be a predictor of long-term renoprotection^[93,94]. However, close care is required to avoid complications such as hyperkalemia or hypotension, which may occur in some patients with deteriorating renal func-

tion and would warrant discontinuation.

The optimism for enhanced efficacy of RAS inhibition by using a combination of ARB/ACE inhibitor has recently dampened. The ONTARGET trial followed 25000 participants (11% Aboriginal/African) with diabetes with end-organ damage (13% with microalbuminuria) or vascular disease for 4.5 years, randomized to Ramipril group (ACE inhibitor), Telmisartan group (ARB), or both^[95]. They found no difference in the composite outcome of cardiovascular events including death or hospitalization for heart failure between groups, and at trend toward increased cardiovascular events in the group receiving combination ARB/ACEI^[95].

TARGET BLOOD PRESSURE IN AFRICAN AMERICANS

The 2007 European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) Guidelines recommended two distinct BP targets: 140/90 mmHg in low-moderate risk hypertensive individuals and 130/80 mmHg in high-risk hypertensive persons (*e.g.*, those with diabetes, cerebrovascular, cardiovascular, or renal disease)^[96]. The 2013 ESH and the ESC Guidelines recommend a blood pressure target of 140/90 mmHg regardless of risk, with a less stringent SBP goal of between 150 and 140 mmHg in the elderly^[2]. They found no evidence to support a lower blood pressure goal (130/80 mmHg) in patients with diabetes or a history of cardiovascular or renal disease^[2]. This was not specific to any racial/ethnic group. This lack of support for a lower blood pressure goal is further supported by the results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial^[97]. The ACCORD trial, which included 19.3% black participants with type 2 DM, used both ACEI and ARB as part of antihypertensive therapeutic approach and found no benefit in regards to major cardiovascular events with a SBP target of < 120 *vs* < 140 mmHg. This is also consistent with the findings mentioned earlier from the AASK trial, which found no differences in clinical outcomes between intensive (\leq 120/80 mmHg) and standard (approximately 135-140/85-90 mmHg) blood pressure targets^[79]. However, the trend toward improved outcomes at a lower blood pressure in patients with elevated baseline protein-to-creatinine ratio > 0.22 (equivalent to baseline protein excretion of > 300 mg/d)^[80], suggests further studies are needed to assess the benefit of a lower target blood pressure in higher risk groups such as African Americans with target organ damage. In fact, based on this and other secondary analyses, the International Society on Hypertension in Blacks consensus statement suggested a BP target of < 130/80 mmHg in hypertensive blacks with target organ damage^[87], although others suggest the data to support such a recommendation is still insufficient^[98].

One of the obstacles to attaining target blood pressure goals in African Americans is the issue of medication adherence. Low medication adherence rates and

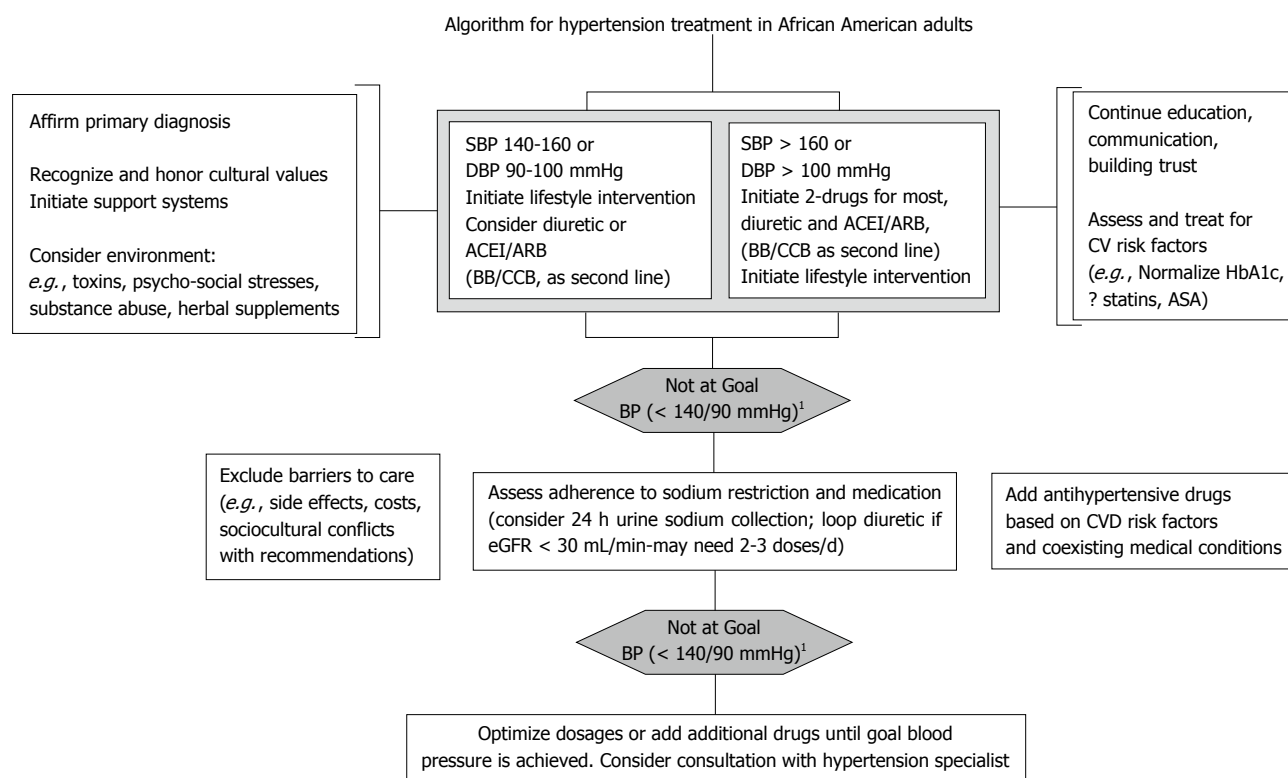


Figure 1 Algorithm for hypertension treatment in African American adults (adapted from ref. [86]). ¹For persons > 60 years of age consider < 150/100 mmHg if initial SBP is > 160 mmHg^[2]. ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; BB: Beta blocker; CCB: Calcium channel blocker; SBP: Systolic blood pressure; CVD: Cardiovascular disease; DBP: Diastolic blood pressure; eGFR: Estimated glomerular filtration rate; CV: Cardiovascular; ASA: Aspirin; ?: Possibly the use of statins or aspirin or possible use of statins or aspirin; BP: Blood pressure.

higher rates of uncontrolled blood pressures are more common in African Americans^[33,99,100]. Keys to the effectiveness of ACEI therapy is adherence to both pharmacologic and non-pharmacologic therapy particularly in African Americans whose lower adherence rates have been attributable to both patient-related and physician-related factors including medication cost, insurance issues and access to healthcare. Aggressive measures are required to target interventions such as patient education focused on patient misconceptions regarding hypertension, home visits by trained community health workers, culturally appropriate storytelling, home blood pressure monitoring and behavioral counseling—all of which have been associated with improved medication adherence and decreased blood pressure measurements in blacks^[100,101].

CONCLUSION

Health care providers currently consider a patient's age, gender and ethnic background when making clinical decisions based on the evidence from clinical research findings. As in the non-African American hypertensive patient, first excluding primary renal or secondary causes of hypertension, then establishing a comprehensive treatment approach, is paramount to slowing the progression of end organ damage (Figure 1). Aggressive treatment of the primary etiology, addressing select lifestyle and socio-cultural issues, and the use of two or more antihyperten-

sive agents for control of blood pressure is typically required in African American patients^[102]. The existing data highly supports the inclusion of RAS blockade agents as initial therapy for African Americans with hypertension. In fact, the data from animal models of salt sensitive, low renin hypertension suggest RAS blockade may be even more imperative in treating African Americans with hypertension than the general population. These agents appear to confer additional end organ protection beyond that offered by other antihypertensive agents in this patient subgroup. Importantly, there is no evidence of reduced efficacy for ACEI or ARB therapy on clinical outcomes in African Americans^[103].

In conclusion, the overall treatment plan should be guided by individual patient response, coexisting risk factors and potential sociocultural considerations such as cost of medications and insurance coverage, which affect adherence to both pharmacologic and non-pharmacologic interventions^[14]. In all racial groups, blood pressure target goals in uncomplicated hypertension based on clinical trial data is < 140/90 mmHg with debate over a lower target (< 130/80 mmHg) in cases with end organ damage due to the data mostly being surrogate markers with a lack of consistent hard outcome data. Further elucidation of the optimal treatment for hypertension may be provided by the ongoing NIH-funded Systolic Blood Pressure Intervention Trial trial which will include a diverse patient population in regards to gender, race/ethnicity

and comorbidities in over 7500 persons over 55 years of age^[104].

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Metabolic syndrome in hypertensive patients: An unholy alliance

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showed that the MetS, even without type 2 diabetes, confers an increased risk of cardiovascular morbidity and mortality in different populations including also hypertensive patients. It is likely that the enhanced cardiovascular risk associated with MetS in patients with high blood pressure may be largely mediated through an increased prevalence of preclinical cardiovascular and renal changes, such as left ventricular hypertrophy, early carotid atherosclerosis, impaired aortic elasticity, hypertensive retinopathy and microalbuminuria. Indeed, many reports support this notion, showing that hypertensive patients with MetS exhibit, more often than those without it, these early signs of end organ damage, most of which are recognized as significant independent predictors of adverse cardiovascular outcomes.

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Key words: Arterial hypertension; Metabolic syndrome; Target organ damage; Cardiovascular risk

Abstract

For many years, it has been recognized that hypertension tends to cluster with various anthropometric and metabolic abnormalities including abdominal obesity, elevated triglycerides, reduced high-density lipoprotein cholesterol, glucose intolerance, insulin resistance and hyperuricemia. This constellation of various conditions has been transformed from a pathophysiological concept to a clinical entity, which has been defined metabolic syndrome (MetS). The consequences of the MetS have been difficult to assess without commonly accepted criteria to diagnose it. For this reason, on 2009 the International Diabetes Federation, the American Heart Association and other scientific organizations proposed a unified MetS definition. The incidence of the MetS has been increasing worldwide in parallel with an increase in overweight and obesity. The epidemic proportion reached by the MetS represents a major public health challenge, because several lines of evidence

Core tip: Several lines of evidence suggest that metabolic syndrome (MetS) may amplify hypertension-related target organ damage (TOD). Some of MetS components, when considered individually may have little or no influence on TOD, but when taken together may synergistically interact promoting the development of left ventricular hypertrophy, aortic stiffness and microalbuminuria. The marked tendency of hypertensive patients with MetS to develop these manifestations of subclinical organ damage, that are well-known predictors of cardiovascular events, largely explain the increased morbidity and mortality associated with the syndrome. Therefore, identifying MetS in hypertensive patients may enable the clinician to better assess the cardiovascular risk.

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INTRODUCTION

For many years, it has been recognized that high blood pressure is often associated with various anthropometric and metabolic abnormalities including abdominal obesity, elevated triglycerides, reduced high-density lipoprotein (HDL) cholesterol, glucose intolerance and insulin resistance.

Several lines of evidence support the notion that these traits occur simultaneously to a greater degree than would be expected by chance alone. This evidence supports the existence of a discrete disorder meriting in the appellation as a “metabolic syndrome”. A variety of clinical and biohumoral alterations may co-exist with the main components of the metabolic syndrome: hyperuricemia, increases in apolipoprotein B and small dense low-density lipoprotein cholesterol, prothrombotic factors, chronic low grade inflammation, non-alcoholic fatty liver disease and/or non-alcoholic steatohepatitis, obstructive sleep apnoea and polycystic ovarian disease. Many of these conditions may contribute to explain why the metabolic syndrome (MetS) conveys an increased risk of developing subclinical and overt cardiovascular and renal diseases.

METABOLIC SYNDROME DEFINITIONS

In the effort to introduce the MetS into clinical practice, several scientific organizations have attempted to formulate working definition of the syndrome. The first proposals came in 1998^[1] and in 1999^[2] from a consultation group on the definition of diabetes for the World Health Organization (WHO)^[2]. Alternative definitions have been proposed subsequently by the European Group for the Study of Insulin Resistance (EGIR)^[3], the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III)^[4] the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI)^[5], the American Society of Clinical Endocrinologists (AACE)^[6] and the International Diabetes Federation (IDF)^[7]. Recently, IDF, AHA/NHLBI and other scientific societies, in an attempt to unify discordant criteria between previous definitions of MetS, proposed a new “harmonizing” definition of this syndrome^[8]. All definitions include a measure of blood pressure (BP), triglycerides, HDL cholesterol, and fasting glucose. They differ with respect to the selection of cutoff points and a measure of obesity. In contrast to the glucocentric approach of the WHO and EGIR definitions, in which the presence of insulin resistance is the starting

point, the ATP III definition is based on the number of abnormalities only, whereas the AACE definition considers the number of abnormalities in selected subjects with high risk of insulin resistance. The ATP III and WHO definitions implicitly include type 2 diabetes (T2DM) as syndrome traits. Not all experts agree that T2DM should be part of the definition, as the importance of the syndrome is that it identifies patients at increased risk for the development of diabetes^[8,9].

Among the various definitions proposed the most widely used is that of the ATP III or the AHA/NHLBI version, that slightly revised the former by lowering the threshold for fasting glucose from 110 to 100 mg/dL.

The wide use of these definitions is due primarily because they provide a relatively simple approach for diagnosing MetS by employing easily measurable risk factors.

In the revised ATP III definition^[5], MetS is diagnosed when at least three or more of the following abnormalities are present: BP $\geq 130/85$ mmHg (or drug treatment for hypertension), HDL < 1.0 mmol/L (40 mg/dL) in men or < 1.3 mmol/L (50 mg/dL) in women (or drug treatment for reduced HDL); fasting glucose ≥ 5.6 mmol/L (100 mg/dL) (or drug treatment for elevated glucose); triglycerides > 1.7 mmol/L (150 mg/dL) (or drug treatment for elevated triglycerides); and waist circumference > 102 cm in men or > 88 cm in women^[5].

On 2005 the IDF has proposed a set of criteria that are similar to those of the updated ATP III criteria. In fact, thresholds are identical for triglycerides, HDL-C, BP, and plasma glucose. The major difference is that the IDF considered central obesity, as assessed by waist circumference (WC), essential for diagnosis. Moreover, in this obesity-centric definition the WC cutoffs were adjusted for different ethnic groups, taking into account that the risk associated with a particular waist measurement (especially for diabetes development) will differ in different populations. But despite the attempt to standardize clinical definition of MetS, this has led to some confusion on the part of clinicians regarding how to identify patients with the syndrome.

Thus came the initiative of the IDF and the AHA/NHLBI, joined by the World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity^[8], to develop one unified definition.

The main difference between the ATP III and the IDF diagnostic criteria is that in the IDF definition abdominal obesity is a prerequisite of the diagnosis of MetS. As a major step in consensus, this obligation has been reversed; therefore the “harmonizing” definition is identical to the revised ATP III definition except that IDF waist circumference cut points were used^[8]. In Europeans (white people of European origin, regardless of where they live in the world) WC thresholds were the same as that used by the EGIR (≥ 94 cm for males and ≥ 80 cm for females), and lower than the ATP III recommendations^[7]. For the Asian people IDF adopted even lower cutpoints for men (≥ 90 cm) and the same as for Europ-

ids for women.

Similarly to adults, no general consensus exists regarding the definition of MetS in children and adolescents^[9,10]. Furthermore, studies published so far have used their own set of variables, number of criteria (three or four) and different cut-off points to define risk factors associated with MetS. In 2007, a consensus report was published by the IDF group^[10], including three age groups: 6 to < 10, 10 to < 16 and 16 + years (adult criteria).

Based on this report, obesity is defined as WC \geq 90th percentile, or adult cut-off if lower, while all other parameters are defined based, rather than percentiles, on absolute numbers, that are the same used for adults^[10].

A scientific statement from the AHA and other scientific societies, published on 2009, called attention to the fact that, especially during adolescence, a marked instability exists in the categorical diagnosis of MetS. This instability, which includes both gain and loss of the diagnosis, suggests that the syndrome has reduced clinical utility in adolescence^[9].

IS METABOLIC SYNDROME REALLY A SYNDROME?

Some controversy also exists about whether the MetS is a true syndrome or a mixture of unrelated phenotypes.

Two major health organizations in Europe (the European Association for the Study of Diabetes) and the United States (American Diabetes Association) have claimed that the MetS is not a single pathophysiological entity, that its identification has no clinical utility, and that clinical emphasis should rather be placed on effectively treating any cardiovascular (CV) risk factor that is present^[11,12]. We believe, together with many experts on CV risk^[8,13,14], that this clustering of interrelated metabolic risk factors is a useful construct, and although it needs to be better defined, represents a good basis for calling this as a syndrome. The rationale supporting use of the MetS includes the following: (1) the label of MetS seems to be an important way to educate patients about the connection between their lifestyle, health risks, and medical outcomes; (2) it provides a framework for research exploring a possible unifying pathophysiological basis for the observed cluster of risk factors; (3) it quantifies chronic disease risk within populations and facilitates between-country comparisons; (4) it can guide relative risk prediction and clinical management decisions; (5) it results from the association of individuals components that are often defined by values that are lower than those meeting the definition of risk factors by many guidelines, which may thus fail to detect the presence of a high CV risk in several subjects with MetS; and (6) it provides an easily comprehensible public health message and reminds health professionals of the need to assess related risk factors when one risk factor is detected ultimately helping implementation of CV prevention^[8,9].

On the other hand, the criteria used to diagnose the

MetS have major limitations including: the dichotomization of risk factors; the attribution of relative as opposed to absolute risk; the differing predictive value of risk factor combinations; the inclusion of individuals with established diabetes and heart disease^[9,10].

PREVALENCE OF METABOLIC SYNDROME IN GENERAL POPULATION AND IN HYPERTENSIVE PATIENTS

The prevalence of the MetS is at least in part dependent on the definition of the syndrome and its components and on the composition (sex, age, race, and ethnicity) of the population studied^[14-27]. However, there is a strong epidemiological evidence that, regardless of the criteria used, the prevalence of MetS is high and rising in all western society and in Asia, very likely as a result of obesity epidemic^[14-20]. In general, it has been estimated that approximately 10%-30% of the world's adult population has the MetS^[14]. A very consistent finding in all of these studies is that the prevalence of the MetS is highly age-dependent^[14-19]. Data regarding gender effect on MetS prevalence are conflicting with the majority of the studies finding the highest prevalence in women compared to men^[14-19]. The conflicting results with respect to gender effect may partly be explained by the application of different definitions for the MetS. The application of the modified WHO criteria tends to increase the prevalence of MetS in men^[18,19].

Since high BP is a key component of MetS, it is not surprising that in MetS patients arterial hypertension is highly prevalent. The Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) population study revealed that high normal BP values and hypertension were present in 80% of individuals with MetS^[21]. Conversely, the prevalence of MetS is more elevated in hypertensive patients than in general population^[18-20,22-36].

In a large French population, the prevalence of MetS was 5.4% ($n = 1181$) among normotensive men and 2.8% ($n = 360$) among normotensive women, and rose to 19.3% ($n = 3490$) for hypertensive men and 14.8% ($n = 1200$) for hypertensive women. Much higher prevalences were reported in other studies performed only in hypertensive patients^[23-36].

In the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) study, a prospective observational investigation of 1742 Italian adult subjects with essential hypertension, MetS, defined according to ATP III criteria, was diagnosed in 34% of the population^[25].

Similar data were obtained in our cross-sectional study conducted in 353 essential hypertensives and 37% of whom had MetS^[26]. In our study population, prevalence of MetS was higher in women than it was in men. This greater proportion of women with MetS was explained by a higher prevalence of visceral obesity and of low HDL values in females when compared to males^[26].

An even greater prevalence of MetS was observed

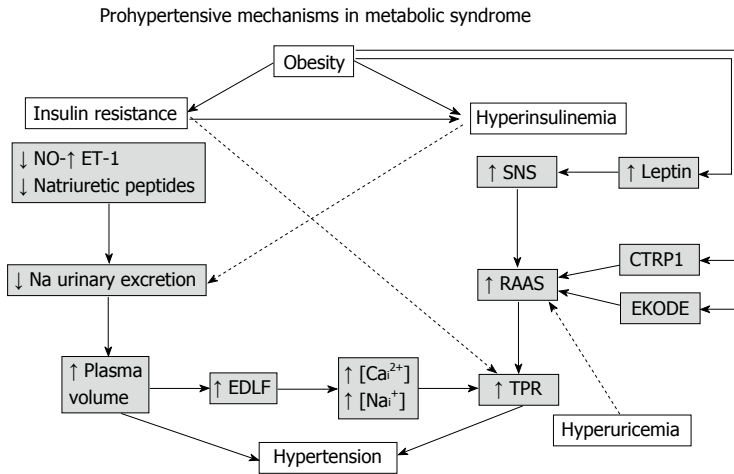


Figure 1 Hypothetical mechanisms by which the metabolic syndrome may lead to high blood pressure. NO: Nitric oxide; ET-1: Endothelin-1; SNS: Sympathetic nervous system; RAAS: Renin-angiotensin-aldosterone system; CTR1: Complement-C1q tumor necrosis factor-related protein 1; EKODE: Epoxy-keno derivative of linoleic acid; TPR: Total peripheral resistance; EDLF: Endogenous digoxin-like factor; $[Ca^{2+}]$: Intracellular concentration of calcium; $[Na^+]$: Intracellular concentration of sodium.

in the Global Cardiometabolic Risk Profile in Patients with hypertension disease (GOOD) study^[33]. This was an observational, cross-sectional survey conducted in 305 sites in 12 European countries. Among the 3370 outpatients included in the analyses 58% had the MetS. This very high prevalence is probably explained by the older age (61 years) of the study population when compared to those of the other investigations conducted in hypertensive subjects. In the same survey it was noticed that the proportion of patients with uncontrolled BP was significantly higher among the subjects with MetS compared with those without it ($P < 0.001$)^[33]. Analogous results were found among the hypertensive population of the Korean National Health and Nutrition Examination Survey^[34] and in the Renal Dysfunction in Hypertension (REDHY) study. In the latter investigation, where a total of 1856 Sicilian hypertensive individuals, free from diabetes mellitus were enrolled^[35], a significantly higher ($P < 0.001$) percentage of patients with uncontrolled BP ($> 140/90$ mmHg) were found in the group with MetS (79%) as compared to the subjects without MetS (71%).

It has been also reported a high frequency of resistant hypertension among individuals with MetS^[36], that can be attributed to a number of pathophysiological mechanisms^[36] that will be described in the following section.

The prevalence of the MetS is growing worldwide^[14-17]. Between 2008 and 2010, the proportion of the hypertensive population with MetS was forecast to increase to 78%, 45% and 43% in Germany, Spain and Italy respectively^[16]. All MetS components were forecast to rise with the prevalence of abdominal obesity and impaired fasting glucose increasing the most. Total annual costs of hypertension with MetS amounted to €24427, €1909 and €4877 million respectively in Germany, Spain and Italy in 2008. By 2020, keeping costs set at 2008 prices, these annual costs of hypertension with MetS were forecast to rise by 59%, 179%, 157% in Germany, Spain and Italy

respectively. The largest component of the total annual economic burden of hypertensive patients with MetS was the treatment and management of the consequence of disease rather than the management of hypertension itself including physician and drug costs^[16].

Pathophysiology of hypertension in metabolic syndrome

Several mechanisms have been hypothesized to explain why the MetS may be considered as a prohypertensive state^[32] (Figure 1).

Although further research is required to better understand the pathophysiology behind the syndrome and the gene-environment interactions that increase susceptibility, there is general agreement that visceral obesity and insulin resistance (IR) are at the core of most cases of MetS^[1-6,37,38]. It is widely believed that IR results from a combination of genetic and environmental factors^[1-6]. Resistance to insulin-mediated glucose disposal determines a compensatory hyperinsulinemia, which serves to maintain glucose homeostasis. However, this initially adaptive mechanism ultimately may promote hypertension and various atherogenic processes. It is only after the pancreas is unable to meet the increased demand for insulin necessary to overcome IR that glucose control becomes abnormal. Therefore, hyperglycemia signifies a more advanced stage in the loss of normal glucose homeostasis^[1-6].

About 50% of patients with essential hypertension are insulin-resistant^[18-20,39-41]. Independently of body mass index, hypertensive individuals, when compared with healthy normotensive controls, have higher fasting and postprandial insulin levels, and greater reductions in insulin sensitivity^[39-42].

Insulin, in response to states of over-nutrition, stimulates the sympathetic nervous system (SNS) to promote thermogenesis and to minimize weight gain. The insulin-mediated hyperadrenergic state, however, leads to an increase in heart rate, and BP^[37,43,44].

Other factors may contribute to the sympathetic activation occurring in MetS. They include leptin, which increases in obesity and has been shown to act as a powerful sympathostimulator^[36,43-46]. Sleep apnoea, which frequently occurs in obesity, may also play a role because its sympathoexcitatory effect *via* the hypoxic activation of the chemoreceptor reflex^[44,46,47].

The enhanced SNS activity and insulin and leptin *per se*^[48] stimulate renal sodium absorption leading to volume expansion and further elevation of BP^[36,43-46] (Figure 1).

Moreover, insulin can cause an upregulation of angiotensin II type I receptors by post-transcriptional mechanisms such as stabilization of receptor mRNA and prolongation of its half life^[49]. The increase in angiotensin II type I receptors potentiates the physiologic actions of angiotensin II that include peripheral vasoconstriction and plasma volume expansion. Furthermore, overexpression of systemic as well as local adipose tissue renin-angiotensin-aldosterone system (RAAS) has been documented in obese persons^[36,45,46,50,51].

The increased activity of RAAS in subjects with MetS may be related also to vitamin D deficiency. Indeed, vitamin D status has been inversely associated with MetS^[52,53].

Experimental studies have suggested that vitamin D may exert its beneficial effects by stimulating the expression of insulin receptor to improve insulin responsiveness for glucose transport or by controlling calcium influx, which is essential for the insulin mediated intracellular process in insulin responsive tissues^[53].

In some studies, increased plasma aldosterone concentrations (PAC) have been reported in obese subjects. These elevated aldosterone levels are often out of proportion to the increase in renin activity^[46,54-58]. Indeed, it has been demonstrated that a variety of adipose tissue-derived factors can stimulate aldosterone synthesis^[36,46,55,57]. Goodfriend *et al*^[55] reported that an epoxy-keto derivative of linoleic acid (EKODE), one of the oxidized products of fatty acids, stimulates aldosterone secretion in rat adrenal cells. More recently, *in vitro* experiments documented that human adipocytes secrete potent mineralocorticoid releasing factors. Among these a Complement-C1q tumor necrosis factor-related protein 1 (CTRP1) is able to increase aldosterone production in cultured human adrenal cortical cells, and serum CTRP1 expression was higher in a small number of hypertensive patients compared with healthy volunteers^[57,58].

On the other hand, the low levels of plasma natriuretic peptides observed in individuals with obesity and MetS might predispose to increased adrenal production of aldosterone, because the stimulatory effect of EKODE on aldosteronogenesis is inhibited by natriuretic peptides^[57]. Another putative mechanism explaining augmented PAC may be endothelin 1^[59-61], which is increased in insulin resistance states^[59-61].

Moreover, insulin resistance and the accompanying compensatory hyperinsulinemia may contribute toward increasing PAC, because insulin is known to stimulate aldosterone synthesis *in vitro*^[62] and reciprocal relation-

ships between aldosterone, insulin resistance and hyperinsulinemia have been described in clinical studies^[36,63,64] (Figure 1).

Adipocytes appear to have all the components of the RAAS and thus may produce locally generated angiotensin II and aldosterone^[36,46,50,51]. On the other hand, increased intrarenal pressure accompanying perirenal fat deposition in obesity contributes to the increased activity of RAAS^[45].

Insulin resistance/hyperinsulinemia and visceral obesity appear to predispose patients to impaired peripheral glucose utilization and nitric oxide (NO) production^[65,66]. Indeed, insulin is a mediator of important vasodilatory functions on the vasculature. In obese individuals with insulin resistance, these functions are lost or even reversed leading to impaired vascular relaxation and hypertension^[65,66]. The underlying mechanism may be an impairment of NO-mediated vasodilation and a relative increase in the activity of endothelins^[59,60,65,66]. Cellular response to insulin is mediated by means of 2 pathways: phosphatidylinositol (PI3) 3-kinase and mitogen-activated protein (MAP) kinase^[65,66]. Activation of the PI3 kinase pathway is associated with the metabolic effects of insulin, including glucose transport, and NO-synthesis, whereas MAP kinase activation is associated with mitogenic effects, such as cell growth and proliferation. It has been demonstrated that in the setting of insulin resistance or T2DM, insulin had reduced effects on PI3 kinase-mediated pathways, while maintaining MAP kinase activity^[65,66].

Furthermore, the increased peripheral vascular resistance that often accompanies insulin resistance may be due in part to altered divalent cation metabolism ("cation imbalance") of vascular smooth muscle cells (VSMC)^[39,67]. One mechanism by which insulin, and its homologous peptide insulin-like growth factor-1 (IGF-1), attenuate vascular contractility is through effects on VSMC divalent cation metabolism^[67]. These hormones reduce Ca^{2+} influx into VSMCs in conjunction with reductions in VSMC contractile responses. It is thought that the mechanism by which insulin and IGF-1 decreases VSMC intracellular Ca^{2+} vasoconstriction is through stimulation of the Na^{+}/K^{+} -ATPase pump^[67]. It has been demonstrated that insulin/IGF-1 activation of the PI3-kinase pathway is critical for the ability of these peptides to stimulate the pump^[67]. Thus, altered PI3-kinase responses to insulin/IGF-1, described in insulin resistance states, may explain the decreased ability of those peptides to mediate vasodilation in insulin-resistant patients^[67]. As angiotensin II has been shown to interfere with PI3 activation in VSMC and cardiomyocytes, overexpression of the tissue RAAS may be one of the major factors in cardiovascular insulin/IGF-1 resistance^[50,51,67,68].

Other factors may contribute to reduce the activity of Na^{+}/K^{+} -ATPase pump in patients with MetS, such as the increased production of the endogenous digoxin-like factor^[68,69]. Elevated plasma levels of this substance have been documented in obese hypertensives with glucose intolerance^[69] and in several circumstances characterized

by volume expansion^[68]. This Na^+/K^+ -ATPase inhibitor promotes natriuresis but also produces accumulation of intracellular sodium, reducing in turn the sodium-calcium exchange system, and increasing cytosolic free calcium^[68]. The cation imbalance may lead to enhanced VSMC contraction and to an elevation of peripheral vascular resistance. Moreover, reducing the sodium pump activity may exaggerate neural stimulation and norepinephrine overflow, which might contribute to increase BP^[68].

On the other hand, the low levels of plasma natriuretic peptides observed in obese and overweight individuals, especially in those with IR^[70] may also predispose to salt retention and increased activation of the sympathetic and renin-angiotensin systems, leading to persistent BP elevations in patients with MetS^[36,46,70] (Figure 1).

Patients with MetS have often raised levels of serum uric acid (SUA)^[6,71]. Hyperuricemia has been usually attributed to hyperinsulinemia and IR in MetS^[6] and is not acknowledged as a main mediator of MetS, and CV diseases (CVD) development. However, investigations conducted in the last decades have changed this traditional view, supporting the concept of an independent link between hyperuricemia and increased risk of MetS, diabetes, hypertension, kidney disease and CV disorders^[71-74]. Pharmacologically induced mild-to-moderate hyperuricemia, *via* oxonic acid administration, in rats resulted in the development of high BP^[72,73]. Experimental studies suggest that SUA might play a role in initiating hypertension through multiple mechanisms, including induction of oxidative stress, activation of RAAS and inhibition of NO^[72]. A plausible common pathway for the above mechanisms is the development of renal arteriolar disease with interstitial macrophage and T-cell infiltration, eventually leading to renal vasoconstriction and ischemia^[72]. Subsequent studies showed that the hypertension developed in 2 phases. Initially, reducing SUA with either xanthine oxidase inhibitors or uricosuric agents could directly reverse the hypertension. Hypertension during this (salt-resistant) phase was mediated by uric acid-dependent activation of the RAAS, by the induction of oxidative stress, and by the reduction in endothelial NO levels^[72]. Over time the animals developed significant renal microvascular disease and tubulointerstitial inflammation, and the hypertension became kidney-dependent and salt-sensitive and persisted despite allowing uric acid levels to return to baseline levels^[73].

Lowering SUA with either allopurinol or probenecid has been shown to markedly reduce BP in pilot studies of adolescents with hypertension or prehypertension, whereas effects on adults with primary hypertension are less prominent^[72,73]. More recently, in 2045 participants of the PAMELA study, elevated SUA levels predicted new-onset home and ambulatory hypertension as well as cardiovascular and all-cause mortality^[74]. There are also studies that suggest SUA may not play a role in hypertension and related disorders^[73,75,76]. One of the strongest

arguments is based on gene wide association studies, which have been able to link polymorphisms in urate transporters with hyperuricemia and gout but not with high BP^[73]. Therefore, despite the findings obtained in animals studies and in adolescents, the question regarding the exact role of uric acid in inducing hypertension and CV diseases remains unanswered.

All the above-described prohypertensive mechanisms may provide the explanation of a common pathophysiological feature observed in patients with MetS that is sodium sensitivity. Chen *et al.*^[77] evaluated the association between MetS and salt sensitivity of BP in 1906 subjects (with and without MetS). Study participants received a low-sodium diet (3 g sodium chloride per day) for 7 d, followed by a high-sodium diet (18 g sodium chloride per day) for an additional 7 d^[77]. They found that: multi-variable-adjusted mean changes in BP were significantly greater in participants with MetS than in those without on both low-sodium and high-sodium diets^[77].

These results support the notion that patients with MetS, especially those with obesity, are very sensible to sodium intake^[36,45,46].

METABOLIC SYNDROME AND CARDIOVASCULAR RISK

The high prevalence of the MetS is of considerable concern because several studies suggest that people with the MetS are at increased risk for developing T2DM^[18-20,78] and CV events^[18-22,25,27,29-32,78-82].

The ability of MetS to predict the development of T2DM has been examined in numerous studies; it was estimated that the MetS approximately quintuples the risk for incident T2DM^[14,78].

About a hundred longitudinal studies were performed in order to assess the CV prognostic impact of the MetS^[18-22,25,27,29-32,82] and the vast majority of them were included in the four meta-analyses carried out up to now summarizing this issue^[78-81].

The most recent and largest of them was that of Mottillo *et al.*^[81] that included near one million patients (total $n = 951083$). The MetS, defined according to the ATPIII criteria, was associated with a 2-fold increase in risk of CVD, CV mortality, myocardial infarction and stroke, and a 1.5-fold increase in risk of all-cause mortality^[81].

Whether or not the prognostic significance of the MetS exceeds the risk associated with the sum of its individual components is still a matter of debate. Even if a number of studies support the notion that diagnosing the MetS adds nothing beyond each individual risk factor for predicting CVD^[11,12], other investigations^[8,20], such as the METS-GREECE Multicentre study, seem to suggest the opposite^[82]. More recently, in the 19257 hypertensive patients randomized in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm MetS was significantly associated with coronary outcomes, stroke, and all-cause mortality after adjusting for age, sex, and

Table 1 Prospective studies exploring the association of metabolic syndrome with cardiovascular events and all-cause mortality in hypertensive subjects

Ref.	No. of subjects (population)	Mean follow-up (yr)	Mean age (yr)	MetS (%)	MetS definition	T2DM (%)	Risk of all-cause mortality	Risk of CV events
Schillaci <i>et al</i> ^[25]	1742 (Italian hypertensives without CVD at baseline)	4.1	50	34.0	Modified ATP III	6.0	Not reported	HR = 1.73 (1.25-2.38) Cardiac events: HR = 1.48, (1.01-2.27). Cerebrovascular events: HR = 2.11 (1.27-3.50) After exclusion of T2DM HR = 1.43 (1.02-2.08)
Pierdomenico <i>et al</i> ^[27]	802 (Italian hypertensives without T2DM, TOD and CVD at baseline)	6.9	53	27.2	Modified ATP III	0	Not assessed	HR = 2.64 (1.52-4.58)
Andreadis <i>et al</i> ^[29]	1007 (Greek hypertensives without CVD at baseline)	2.1	59	42.1	Modified ATP III	13.2	Not assessed	HR = 1.75 (1.15-2.66) Cardiac events: HR = 1.73 (1.00-3.00). Cerebrovascular events: HR = 1.91 (1.01-3.58) After exclusion of T2DM: HR = 1.67 (1.01-2.74)
Zanchetti <i>et al</i> ^[28]	2034 (European hypertensives participating in the ELSA study)	3.7	56	33.3	Modified ATP III	4.5	Not assessed	Incidence of CV events not different (about 6% in subjects with and in those without MetS)
Pannier <i>et al</i> ^[22]	26447 French hypertensives without CVD at baseline	4.1	50	17.8	ATP III	Not reported	HR = 1.40 (1.13-1.74)	Not assessed
de Simone <i>et al</i> ^[30]	8243 hypertensives with EKG-LVH participating in the LIFE study	4.8	67	19.3	Modified ATP III	12.5	Not assessed	HR = 1.47 (1.27-1.71) CV death: HR = 1.73 (1.38-2.17)
Vlek <i>et al</i> ^[31]	1815 hypertensives with CVD at baseline and without T2DM	3.9	61	42.7	ATP III	0	Not assessed	HR = 1.24 (0.95-1.62) CV death: HR = 1.41 (1.01-1.98)
Gupta <i>et al</i> ^[32]	19257 hypertensives participating in the ASCOT-BPLA study	5.5	63	43.8	ATP III	27.0	HR = 1.35 (1.16-1.58) ¹	Stroke: HR = 1.34 (1.07-1.68) ¹ MI: HR = 1.16 (0.95-1.43) ¹

¹HR are adjusted for the individual components of MetS. MetS: Metabolic syndrome; CVD: Cardiovascular disease; ATP III: Third report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults; T2DM: Type 2 diabetes mellitus; TOD: Target organ damage; CV: Cardiovascular; MI: Myocardial infarction; EKG-LVH: Left ventricular hypertrophy detected by electrocardiography; ELSA: European Lacidipine Study on Atherosclerosis; LIFE: Losartan Intervention For Endpoint reduction; ASCOT-BPLA: Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm.

ethnicity. However, when the model was further adjusted for the individual components, MetS was associated with significantly increased risk of stroke and all-cause mortality but not coronary disease (Table 1)^[32].

The adverse prognostic impact of the MetS, in hypertensive patients was also observed in other six investigations (Table 1)^[22,25,27,29-31]. In the aforementioned PIUMA study, hypertensive participants with MetS had an increased risk of developing cardiac and cerebrovascular events, independently of traditional CV risk factors, including left ventricular (LV) hypertrophy (LVH) and 24-h BP^[25]. Most notably, the association between the MetS and future CV morbidity also held in patients without diabetes mellitus at the baseline examination^[25].

In contrast with these studies, in the European Laci-

dipine Study on Atherosclerosis study, a large cohort of well-treated hypertensive subjects, outcomes were not different between patients with MetS and those without it^[28], probably because an effective antihypertensive treatment may largely counteract the detrimental influence of MetS (Table 1).

It is conceivable that the increased CV risk conferred by MetS in hypertensive subjects may in part be mediated through preclinical cardiac and renal organ damage. Indeed, major CV events in most hypertensive patients are preceded by the development of asymptomatic cardiovascular and renal structural and functional abnormalities^[83], most of which are recognized as significant independent predictors of adverse cardiovascular outcomes^[84-87].

Table 2 Cross-sectional studies investigating the association of metabolic syndrome with various markers of subclinical organ damage

Ref.	No. of subjects (population)	LVM	LV diastolic function	Carotid IMT and plaques	Micro- albuminuria	CKD	Arterial stiffness
Mancia <i>et al</i> ^[21]	2051 (Italian GP)	↑	-	-	-	-	-
Cuspidi <i>et al</i> ^[23]	447 (Italian hypertensives)	↑	-	↑	↑	-	-
Leoncini <i>et al</i> ^[24]	354 (Italian hypertensives)	↑	-	↑	↑	-	-
Mulè <i>et al</i> ^[26]	353 (Italian hypertensives)	↑	Impaired	-	↑	-	-
Mulè <i>et al</i> ^[91]	475 (Italian hypertensives)	↑	Impaired	-	-	-	-
Schillaci <i>et al</i> ^[92]	618 (Italian hypertensives)	↑ ¹	Impaired ¹	-	-	-	-
Nicolini <i>et al</i> ^[93]	200 (Italian hypertensives)	↑ ¹	Impaired ¹	-	-	-	-
Aijaz <i>et al</i> ^[94]	2042 (United States GP)	↑ ¹	Impaired ¹	-	-	-	-
Sundström <i>et al</i> ^[96]	820 (elderly Swedish GP)	↑	-	-	-	-	-
de Simone <i>et al</i> ^[97]	2758 (American Indian GP)	↑	Impaired	-	-	-	-
Burchfiel <i>et al</i> ^[98]	1572 (United States Black GP)	↑	-	-	-	-	-
de las Fuentes <i>et al</i> ^[99]	607 (United States GP)	↑	Impaired	-	-	-	-
Hwang <i>et al</i> ^[100]	1599 (South Korean GP)	↑	Impaired	-	-	-	-
Kim <i>et al</i> ^[101]	1886 (South Korean GP)	-	Impaired	=	-	-	↑
Ingelsson <i>et al</i> ^[102]	1945 (United States GP)	↑	-	↑	↑	-	-
Ferrara <i>et al</i> ^[103]	340 (Italian hypertensives)	↑	-	=	-	-	-
Aksoy <i>et al</i> ^[105]	90 (Turkish subjects)	↑	Impaired	-	-	-	-
Mulè <i>et al</i> ^[88]	93 (Italian hypertensives)	-	-	-	-	-	↑
Schillaci <i>et al</i> ^[119]	169 (Italian hypertensives)	-	-	-	↑	-	↑
Scuteri <i>et al</i> ^[120]	20750 (9 cohorts from Europe and United States)	-	-	-	-	-	↑
Scuteri <i>et al</i> ^[121]	6148 (Italian GP aged 14-102 years)	-	-	↑	-	-	↑
Scuteri <i>et al</i> ^[122]	471 (United States GP)	-	-	↑	-	-	↑
Zanchetti <i>et al</i> ^[128]	2034 (European hypertensives)	-	-	↑	-	-	-
Kawamoto <i>et al</i> ^[124]	760 (Japanese patients)	-	-	↑	-	-	-
Irace <i>et al</i> ^[125]	1853 (Italian GP)	-	-	=	-	-	-
Chen <i>et al</i> ^[110]	6217 (United States GP)	-	-	-	↑	↑	-
Chen <i>et al</i> ^[109]	15160 (Chinese GP)	-	-	-	↑	↑	-
Navarro <i>et al</i> ^[111]	8425 (Spanish hypertensives)	-	-	-	-	↑	-
Johns <i>et al</i> ^[112]	574 (United States non-diabetic GP)	-	-	-	-	↑	-

¹Only in women. LVM: Left ventricular mass; IMT: Intima-media thickness; CKD: Chronic kidney disease; =: No difference; ↑: Increased; -: Not evaluated; LV: Left ventricular; GP: General population.

METABOLIC SYNDROME AND HYPERTENSIVE TARGET ORGAN DAMAGE

The very frequent occurrence of BP values in the high normal or frankly hypertension range in subjects with the MetS^[18-21] may explain the increased prevalence of hypertension-related preclinical (or asymptomatic) organ damage, such as LVH, elevated urinary albumin excretion rate and arterial stiffening^[18-21,23,24,26]. Some of these markers of organ damage, however, are frequently observed also in individuals who have the MetS without a BP elevation, or also in hypertensive individuals after adjustment for BP values in multivariate analyses, suggesting that other components of this condition play a role independently of BP^[20] (Table 2).

We performed a cross-sectional study to assess the impact of MetS, defined according to the NCEP-ATP III criteria, on some cardiac, renal and retinal markers of target organ damage (TOD), in 353 non-diabetic young and middle aged essential hypertensives without clinical or laboratory evidence of CV and renal diseases^[26].

In a subset of untreated subjects of the same population, we also explored the carotid-femoral pulse wave velocity (PWV), a measure of aortic stiffness, in patients with and without MetS^[88].

Hypertensive patients with MetS exhibited higher LV mass on echocardiography [either normalized by body surface area (BSA) or by height elevated by a power of 2.7], relative wall thickness, left atrial size, and greater prevalence of LV hypertrophy, lower mid-wall fractional shortening and a longer E-wave deceleration time than subjects without MetS^[26]. These results were maintained even after correction for several confounding variables, such as age, gender distribution, severity and duration of hypertension and previous antihypertensive therapy. In particular, after adjustment for these covariates, the likelihood of LV hypertrophy was 2.89-fold (95% interval, 1.68 to 4.98) higher in subjects with MetS than in those without it, when LV mass was indexed by height^{2.7} (LVMH^{2.7})^[26]. Moreover, the higher the number of components of the MetS, the greater the LVMH^{2.7}^[18]. It is noteworthy that the relationship between MetS and LV mass was confirmed in multivariate regression models, including MetS together with its individual components, as independent variables^[26]; this seems to suggest that MetS may have a deleterious effect on cardiac structure over and above the potential contribution of each single component of this syndrome, and that the confluence of abnormalities that comprise MetS may have a synergistic negative impact on LV mass.

We obtained similar results also when the influence of MetS on cardiac mass was evaluated in white coat hyper-

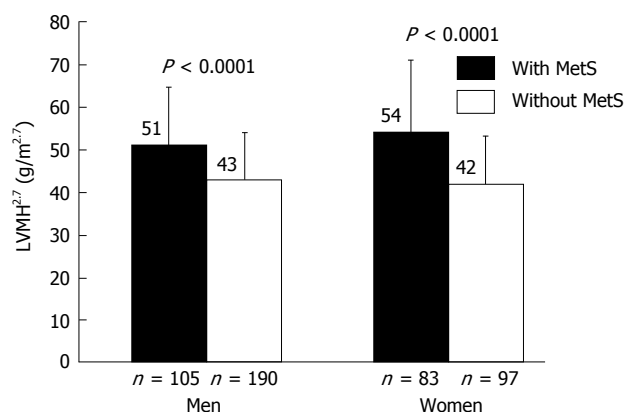


Figure 2 Mean values of left ventricular mass indexed for height^{2.7} in hypertensive men and women with and without the metabolic syndrome^[91]. LVMH^{2.7}: Left ventricular mass indexed for height^{2.7}; MetS: Metabolic syndrome.

tensives^[89], and in a subgroup of overweight and obese hypertensive patients^[90]. On the other hand we did not observe a significant effect modifier of gender on the association between MetS and LV mass^[91], at variance with the results reported in some^[92-94], but not all^[95,96], investigations exploring this issue.

Indeed, we found similar differences, regarding LV mass, in females and males with MetS when compared to their counterparts without the MetS (Figure 2)^[91]. Moreover, in a two-factor ANOVA model, the analysis of the interaction term “gender × MetS” revealed no significant effect of sex on the association between MetS and LV mass, either normalized for BSA or height^{2.7}^[91].

The unfavorable impact of the MetS on cardiac structure was confirmed in a large number of cross-sectional studies, conducted in different ethnic groups, in general populations^[97-102], as well as in hypertensive patients^[18-20,103] (Table 2). Moreover, it was even more convincingly demonstrated by the population based PAMELA study, in which the subjects with MetS had a three fold risk to develop LVH, than those without it, during a ten years follow-up period^[104].

The putative mechanisms by which MetS promotes LVH^[18,19] are summarized in Figure 3. It is interesting to note that a variety of studies suggest that LV diastolic function may be adversely influenced by the MetS *per se*^[99-101], even in the absence of diabetes and hypertension and in part independently of age and left ventricular mass^[105].

The asymptomatic changes in cardiac structure and function induced by the MetS largely explain why this syndrome is a powerful independent predictor of subsequent heart failure (HF), even after adjustment for established risk factors for HF^[106,107]. This increased HF risk may be in part promoted by insulin resistance and accompanying hyperinsulinemia that may have direct myocardial effects in addition to its proatherosclerotic effects. Indeed, in the Uppsala Longitudinal Study of Adult Men, insulin resistance, measured with the reference standard euglycaemic insulin clamp technique, was an independent

risk factor for HF, taking diabetes, obesity and other potential confounding factors into account^[108].

There are other important findings from our study that deserve special mention: hypertensive subjects with MetS compared to those without it showed greater level of albumin excretion rate and consequently higher prevalence of microalbuminuria^[26], that is nowadays considered, not only a predictor of renal complications, but also a harbinger of premature CVD^[86,87]. These results, that we confirmed in the larger population of the above described REDHY study^[35] (Figure 4), are consistent with the findings of other investigations conducted in hypertensive patients^[23,24] and in general populations^[102,109]. In some of these studies^[109] and in other ones^[110-113], with cross-sectional and longitudinal design, a relationship between the MetS and chronic kidney disease was also observed (Table 2).

Another result of our study merits a comment. In keeping with other reports^[114,115], we noted an increased prevalence of grade I and grade II hypertensive retinopathy in subjects with MetS when compared to persons without MetS^[26]. However, because the prognostic implications of early hypertensive retinopathy grades are unclear^[116], the clinical significance of these findings remains undefined.

Unlike the milder forms of hypertensive retinopathy, prognostic value of increased aortic stiffness seems to be more soundly demonstrated; there is an extensive and very consistent body of evidence showing that large artery stiffening is a powerful predictor of CV morbidity and mortality^[85]. Because a fundamental principle states that pulse waves travel faster in stiffer arteries, PWV is the most widely used measure of arterial stiffness. PWV measured along the aortic and aorto-iliac pathway is the most clinically relevant since the aorta and its first branches are responsible for most of the pathophysiological effects of arterial stiffness^[85]. Therefore, aortic PWV is regarded as the gold standard measurement of arterial stiffness.

When we assess the influence of MetS on aortic PWV in a sample of never treated non-diabetic patients with essential hypertension, we found more elevated PWV in subjects with MetS when compared to those without it^[88].

These data, that we recently replicated in a wider group of hypertensive patients (Figure 5), are in line with the results we observed in another cross sectional study carried out in 528 nondiabetic patients (age 18 to 72 years) with essential hypertension^[116]. We found that, when compared with subjects without MetS, hypertensive patients with MetS exhibited more elevated clinic and 24-h pulse pressures that may be considered as a proxy for arterial stiffness, especially in older subjects. The difference held even after correction for age, sex, stroke volume, mean pressures, and total cholesterol^[116]. The regression line relating PP with age was steeper in patients with MetS than in those without MetS (Figure 6), suggesting that arterial aging is faster in the former as compared to the latter^[117].

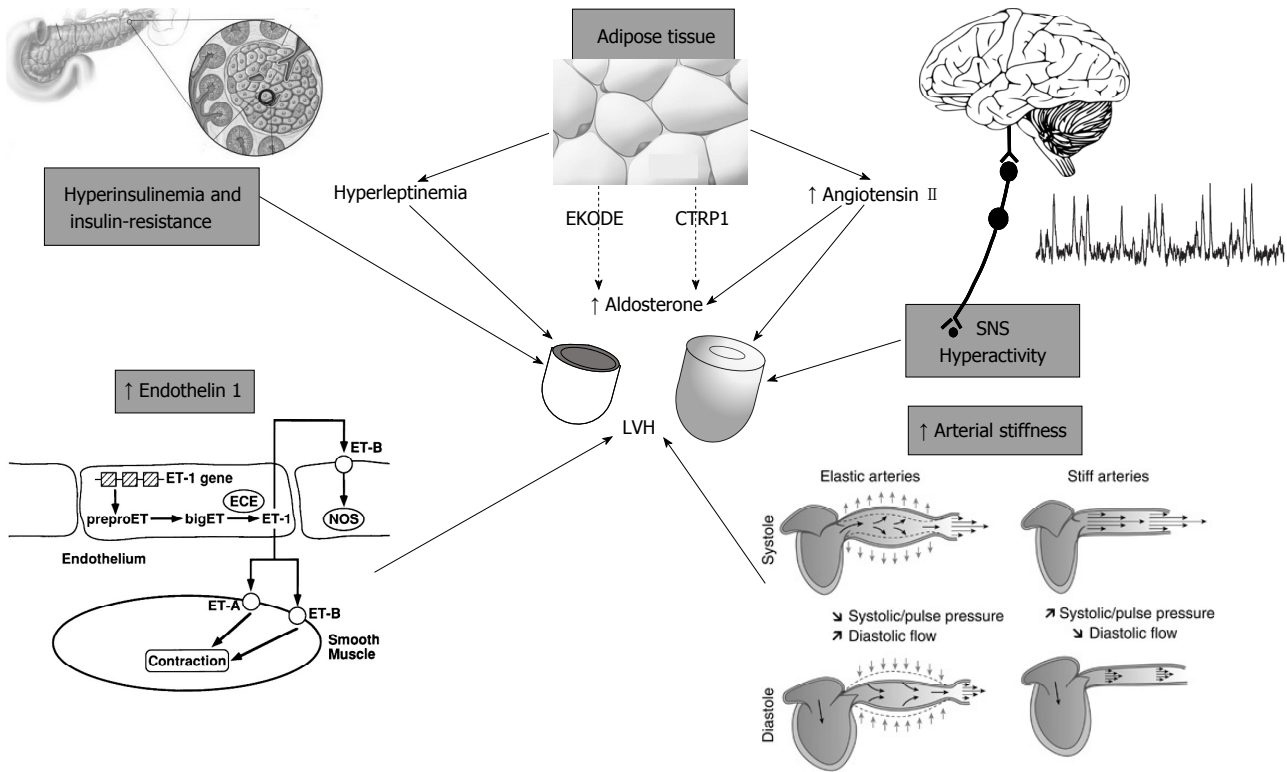


Figure 3 Putative mechanisms by which metabolic syndrome promotes left ventricular hypertrophy. SNS: Sympathetic nervous system; CTRP1: Complement-C1q Tumor necrosis factor-related protein 1; EKOGE: Epoxy-keto derivative of linoleic acid; LVH: Left ventricular hypertrophy.

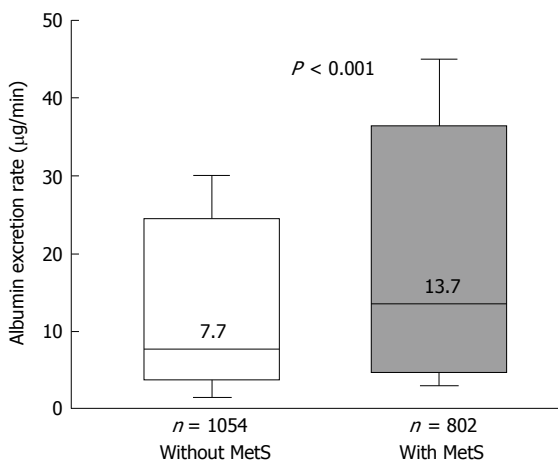


Figure 4 Box plots showing urinary albumin excretion rates in nondiabetic hypertensives participating in the Renal Dysfunction in Hypertension study^[39], divided in subjects with and without the metabolic syndrome. In the Box-and-Whisker plots, the central boxes represent the interquartile range (25th to 75th percentile). The middle lines, and the numbers above these lines, represent the median values. Lower and upper whiskers extend to 5th and 95th percentile. MetS: Metabolic syndrome.

Our observations are in agreement with several lines of evidence^[101,118-122], suggesting that the MetS accelerates the age-related rise in arterial stiffness, leading to a condition defined as early vascular aging (EVA)^[123]. Premature arterial senescence in MetS is biologically plausible. The structural changes occurring during aging in large arteries include extensive impairment of the elastin fiber network, increase in collagen content, calcification of the

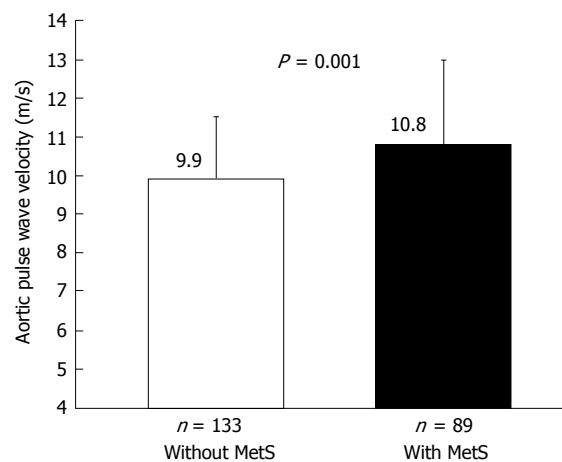


Figure 5 Mean values of aortic pulse wave velocity in untreated hypertensive subjects with and without the metabolic syndrome^[76]. MetS: Metabolic syndrome.

media, and accumulation and migration of VSMC in the arterial walls^[121,123]. In subjects with MetS, these modifications may occur earlier, especially in the aorta, for several reasons: (1) activation of the RAAS, that is involved in regulating the turnover of extracellular matrix proteins and that is a strong regulator of matrix metalloproteinase and tissue inhibitor of metalloproteinases; (2) increase in oxidative stress and chronic low grade inflammation; (3) increased glycation of matrix proteins; (4) decreased endothelial bioavailability of nitric oxide associated with insulin resistance; (5) endothelin-1 increase; (6) elevation

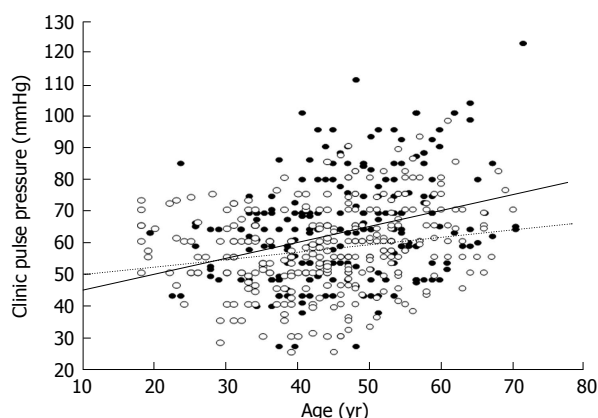


Figure 6 Scatterplot showing the relationship between age and pulse pressure in subjects with (black circles) and in those without (white circles) metabolic syndrome. The calculated regression lines for the former (continuous line) and the latter patients (dotted line) were also shown. The difference regarding the slopes of the two regression lines was statistically significant ($P = 0.01$).

in leptin; and (7) hypoadiponectinemia^[18-20].

EVA, as well as other indices of preclinical organ damage, reflects cumulative damaging effects from risk factors and entails an enhanced risk of CV events and of cognitive dysfunction^[123]. Schillaci *et al.*^[119] in 169 newly diagnosed non-diabetic hypertensive subjects, observed a greater aortic PWV in the subgroup with MetS, whereas upper limb PWV did not differ in the groups with and without MetS. Very recently, Scuteri *et al.*^[120] studied 20570 subjects from 9 cohorts representing 8 different European countries and the United States, participating in the Metabolic syndrome and Arteries REsearch (MARE) Consortium. In this large-scale observational study any cluster of MetS components identified as MetS, with the exception of low HDLc (H) + high triglycerides (T) + abdominal obesity (W), was associated with stiffer arteries than in control subjects^[120]. Overall, the combinations T + elevated BP (B) + W, elevated fasting glucose (G) + B + W, and G + T + B + W were consistently associated with significantly stiffer arteries to an extent similar or greater than observed in subjects with alteration in all the five MetS components, even after adjustment for multiple confounders. Differences in BP levels amongst the clusters of MetS components do not seem to explain the reported difference in the odds of having stiffer arteries^[120]. The results attained in the MARE Consortium concur with those obtained in the SardiNIA Project^[121] and in the Baltimore Longitudinal Study on Aging^[122] where the subject with MetS showed an increased carotid stiffness when compared with subjects without it.

Moreover, the results of these studies support the notion that the MetS accelerates arterial ageing over and above the predicted power of its individual components, in marked contrast with the concept that the MetS does not provide further information in addition to the sum of its components. In the same investigations an association between MetS and carotid intima-media thickness has been observed^[121,122], in accordance with some^[23,24,28,102,124],

but not all studies^[101,125].

A significant association between carotid atherosclerosis and MetS has been reported in participants in the Framingham Offspring study with MetS^[102]. In the same study a greater prevalence of various indices of subclinical CVD (left ventricular hypertrophy by electrocardiography or echocardiography, carotid ultrasound abnormalities, reduced ankle-brachial index, microalbuminuria) was described in subjects with MetS^[102].

Interestingly, individuals with MetS with evidence of subclinical disease experienced a risk of CV events nearly threefold that of participants without subclinical disease. The presence of subclinical disease conferred approximately a two-fold risk of overt CVD even in those without either MetS or diabetes (compared with their counterparts without subclinical disease). Adjustment for subclinical disease presence markedly attenuated the association of MetS with CVD risk^[102]. This observation emphasizes the important role of subclinical disease in mediating the CV risks associated with MetS.

METABOLIC SYNDROME AND HYPERTENSION: THERAPEUTIC IMPLICATIONS

Effective CVD prevention requires that multiple risk factors be addressed simultaneously to obtain the most significant reduction of morbidity and mortality in a given population. From this point of view, the identification of patients with the MetS offers a unique chance of practicing preventive medicine.

Once identified, aggressive treatment of the MetS is crucial to reduce the increased CV risk. Medications are targeted to individual components of the syndrome (Table 3). However, although pharmacological therapy is often necessary, the cornerstone of treating the MetS remains lifestyle modification^[5,20], that represents the only truly holistic therapeutic approach that can reduce insulin resistance and visceral obesity. It involves behavioral counseling, education, dietary changes and increased physical activity, with a goal of ≥ 30 min of moderate-intensity activity on most days of the week^[5,20]. Even modest weight loss (7% to 10% of body weight) results in decreased fat mass, BP, glucose, and triglyceride levels^[5,20]. These benefits can also translate into improved long-term outcome, especially if weight loss and lifestyle alterations are maintained.

A meta-analysis of 50 studies and 534906 individuals showed that adherence to the Mediterranean diet protect against the development of the MetS and its individual components. This dietary pattern, that can be easily followed by various cultures with small modifications, is characterized by the frequent consumption of olive oil, fruits, tree nuts, legumes, whole grains, weekly consumption of fish and poultry, a relatively low consumption of red meat, as well as a moderate consumption of alcohol normally with meal and usually in the form of

Table 3 Therapeutic approaches in patients with metabolic syndrome

Metabolic syndrome component	Goal of therapy	Drugs	Diet	Physical exercise
Arterial hypertension	BP < 140/90 mmHg	ACEI or ARBs and/ or Ca-antagonists and/ or alpha-blockers ¹ Limit diuretics and beta-blockers	Salt restriction and hypocaloric	Regular exercise
Hyperglycemia	HbA1c < 7%-6.5%	Metformin GLP-1-Agonists DPP-4-inhibitors	Hypocaloric	Regular exercise
Obesity	Weight loss 7%-10%	Orlistat Bariatric Surgery	Hypocaloric	Regular exercise
Dyslipidemia	LDL < 100-70 mg/dL TG < 150 mg/dL HDL: Men > 40/ Women > 50 mg/dL	Statins ± ezetimibe. PUFA-n-3, Fibrates	Hypocaloric	Regular exercise

¹Not first choice. BP: Blood pressure; ACEI: Angiotensin converting enzyme inhibitors; ARBs: Angiotensin II receptor blockers; GLP-1: Glucagon-like peptide-1; DPP-4: Dipeptidyl peptidase-4; LDL: Low-density lipoprotein; TG: Triglycerides; HDL: High-density lipoprotein; PUFA-n-3: Omega-3-Polyunsaturated.

red wine^[126]. However, the remaining challenge is how to promote long-term adherence to a healthier, more active lifestyle and avoid reversion to old habits.

The more recent European guidelines for the management of hypertension do not recommend prescribing antihypertensive drugs in subjects with high normal BP, because no evidence is available^[127]. The same guidelines do point out that beta-blockers (except for vasodilating beta-blockers) and diuretics (especially when combined together) may facilitate the development of new onset diabetes and therefore should be avoided as first line therapy in hypertensives with MetS^[127]. When diuretics are employed, low doses should be used, preferably in association with a potassium-sparing drug, because hypokalemia may worsen glucose metabolism^[127].

Unlike beta-blockers and diuretics, newer antihypertensive medications are associated with a reduced (or not increased) risk of incident diabetes^[20,51,127] and they are also associated with better adherence to therapy^[128]. In addition, it has been demonstrated that obese hypertensive patients during weight loss therapy show significantly better weight reduction and improvement of insulin resistance when treated with newer antihypertensive medications compared to the older BP lowering drugs (especially beta-blockers)^[20,65,127]. Of the newer antihypertensive treatments angiotensin receptor blockers (ARBs) have been found to be associated with lowest rate of discontinuation of therapy^[128] and with lowest incidence of new onset diabetes^[129]. Moreover, specific ARBs (telmisartan and to a lesser extent irbesartan) seem to allow a superior control of BP over 24 h, documented also in subjects with MetS^[130] and also a partial peroxisome proliferator-activated receptor- γ agonism not present in other ARBs or ACE-inhibitors (ACEI)^[20,127,131]. However, the clinical relevance of these differences seem to be negligible or uncertain, since in the Ongoing Telmisartan Alone and in Combination with Ramipril Trial, telmisartan was not more effective than ramipril in preventing CV events or delaying onset of diabetes^[127].

The choice of the newer BP lowering drugs, such as the RAAS-blockers and the long-acting calcium antagonists, seems to be particularly recommended in hypertensive patients with MetS, in the light of the above-mentioned marked tendency of these subjects to the development of LVH and stiffening of the large arteries^[18-26]. As a matter of fact, the efficacy of these drugs, in reducing LV mass and arterial stiffness^[127] is greater than the older ones.

Although meta-analyses suggest antihypertensive drugs have a similar effect on reducing CV events^[127], no randomized clinical trial has been specifically performed in hypertensive patients with the MetS, having the aim to test the superiority of one class of BP lowering drugs over another. However, very recently, in the Cardiovascular Health Study, a community-based prospective cohort study conducted by the National Heart Lung and Blood Institute, the association between the use of ACEI/ARBs and incident CV events was evaluated in elderly people with hypertension and MetS^[132]. ACEI/ARBs use was associated with a lower risk of CVD events, primarily due to a reduction in coronary events^[132]. Pending validation from prospective clinical trials, it seems reasonable to say that ACEI/ARBs may be the preferred treatment for hypertension management in patients with MetS.

Newer antihypertensive agents lead to better control of BP in part brought about by better adherence, thereby reducing the risk of CVD. Needless to say that CV events and new onset T2DM are associated with significant social and health costs. Therefore, in patients with hypertension and MetS, some of the drug costs of newer antihypertensive medications will be balanced by costs saved from reducing these negative outcomes.

CONCLUSION

An extensive body of evidence suggests that the MetS may accelerate arterial aging and amplify hypertension-related cardiac and renal changes. Some of the MetS

components, when considered individually may have little or no influence on TOD, but when taken together may synergistically interact promoting the development of LV hypertrophy, LV diastolic dysfunction, aortic stiffness and microalbuminuria. The marked tendency of the hypertensive patients with the MetS to develop these preclinical manifestations of end-organ damage, may largely explain why the MetS entails an increased risk of CV morbidity and mortality, since these markers of TOD are well-known predictors of CV events. Therefore, identifying the MetS in hypertensive patients may enable the clinician to better assess the CV risk. Once this syndrome is properly identified, aggressive implementation of therapeutic lifestyle changes and appropriate medications, able to decrease insulin resistance, hyperinsulinemia and weight gain can greatly reduce its adverse prognostic impact.

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WJC 6th Anniversary Special Issues (1): Hypertension

Management of erectile dysfunction in hypertension: Tips and tricks

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Core tip: The prevalence of erectile dysfunction is approximately 2-fold higher in hypertensive patients compared to normotensive individuals. However, erectile dysfunction remains under-reported, under-recognized, and under-treated in hypertensive patients. Lifestyle modification should be the mainstay of treating erectile dysfunction in patients with untreated hypertension. Switching antihypertensive therapy should be considered in treated hypertensive patients, unless administered drugs are absolutely indicated for the individual patient. Otherwise, phosphodiesterase-5 inhibitors should be used, since they are both effective and safe in hypertensive patients. Finally, erectile dysfunction offers the opportunity to recognize asymptomatic cardiovascular disease with obvious benefits for cardiovascular event prevention.

Abstract

Arterial hypertension is a major risk factor for cardiovascular disease and affects approximately one third of the adult population worldwide. The vascular origin of erectile dysfunction is now widely accepted in the vast majority of cases. Erectile dysfunction is frequently encountered in patients with arterial hypertension and greatly affects their quality of life of hypertensive patients and their sexual partners. Therefore, the management of erectile dysfunction in hypertensive patients is of paramount importance. Unfortunately, erectile dysfunction remains under-reported, under-recognized, and under-treated in hypertensive patients, mainly due to the lack of familiarity with this clinical entity by treating physicians. This review aims to discuss the more frequent problems in the management of hypertensive patients with erectile dysfunction and propose ways to overcome these problems in everyday clinical practice.

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INTRODUCTION

Undoubtedly, heart disease is and will continue to be one of the major health problems of modern society. Approximately one death every forty seconds occurs due to cardiovascular (CV) disease in the United States alone and arterial hypertension is one of the greatest culprits for it^[1]. Considering the fact that around 25% of the global

population suffer from arterial hypertension, predicted to reach 1.5 billion people in the foreseeable future, it is easily deducted that a respectful part of the general population is under major and constant CV risk^[2,3].

In addition, those patients experience a lower health quality and exhibit lower scores in the widely acceptable quality of life parameters. Sexual dysfunction, an acknowledged condition frequently co-existing with hypertension, contributes significantly to the impaired health quality of both hypertensive patients and their sexual partners^[4,5].

An equally valuable observation though, is the fact that sexual dysfunction could indeed indicate asymptomatic CV disease. A solid amount of evidence accumulated over the last years has pointed out towards that trend moving, hesitatingly though, sexual dysfunction in the surface of scientific interest. As such, commonly under-reported, under-recognized and under-treated, sexual dysfunction could indeed play its role in cardiovascular risk assessment and stratification.

Despite physician's inexperience and patient's reluctance to disclose sexual dysfunction problems, attempts to estimate the magnitude of this clinical condition have predicted that over 150 million men worldwide experience some degree of erectile dysfunction. Several studies have demonstrated a wide range regarding the prevalence of erectile dysfunction, which is even higher in patients with essential hypertension where the relative risk is approximately two times higher than in normotensive individuals^[6-11]. The etiology can be found in the structural and functional abnormalities of the penile arteries induced by high blood pressure. Smooth muscle hypertrophy, stenotic lesions due to atherosclerosis and impaired blood flow are among the prominent structural alterations whereas endothelial dysfunction and the defective nitric oxide-induced vasodilatory mechanism belong to the main functional abnormalities induced by increased blood pressure^[12,13]. As a matter of fact, sexual dysfunction is encountered more frequently that it is indeed believed underlining the need for a more proper and concrete assessment.

This review aims to discuss the more frequent problems in the management of hypertensive patients with erectile dysfunction and propose ways to overcome these problems in everyday clinical practice.

UNTREATED HYPERTENSIVE PATIENTS

Vasculogenic sexual dysfunction is the main cause of sexual dysfunction in untreated hypertensive patients. However, due to the complex etiologic and pathophysiologic nature of sexual dysfunction, exclusion of concomitant diseases and drugs should be the initial step when approaching a hypertensive patient with this clinical condition that is not receiving any antihypertensive medication. Consequently, a significant amount of neurological, psychiatric, urologic and endocrine disorders should be ruled out before vasculogenic sexual dysfunction is diagnosed.

When the diagnosis of vasculogenic sexual dysfunction

has been carefully reached, physicians will have to come up with an effective treatment. Appropriate lifestyle measures and adoption of a healthier attitude could represent an initial, efficient and cost-effective treatment option^[14]. This is due to the fact that traditional CV risk factors such as hypertension, physical inactivity-obesity, smoking and dyslipidemia have been consistently linked with endothelial and consequently sexual dysfunction^[15]. In this context, it has been demonstrated that moderate physical activity can reduce up to 30% the risk of erectile dysfunction contrary to sedentary life, which exerts a deleterious effect^[16]. Interestingly, the beneficial effect of physical exercise on sexual dysfunction seems to be independent of its favorable impact on the general cardiovascular profile^[17]. In terms of caloric reduction, Mediterranean diet exerts a positive effect on sexual function parameters of patients with metabolic syndrome^[18]. Moreover, combined physical exercise and caloric restriction can result in weight reduction which in succession can reduce up to 30% the risk of obesity-associated erectile dysfunction^[19].

Whereas lifestyle modification is a reasonable initial step when approaching a hypertensive patient with sexual dysfunction, finding the appropriate antihypertensive treatment is usually the next "complicated" move to care for. Several observational and clinical studies have consistently associated antihypertensive medication with sexual dysfunction^[20]. Whether one class of antihypertensive agents is associated exclusively or more with erectile dysfunction compared to another, however, is a difficult puzzle to solve as there are many other factors (comorbid conditions, concomitant medications, personal characteristics) to be taken into account at the same time. In addition, erectile dysfunction has never been studied as the primary end-point before and as a result a definite causative relationship between antihypertensive medication and sexual dysfunction has never been proven.

Despite the existing controversies, available data so far imply the old generation b-blockers (*e.g.*, propranolol) as the major culprits for sexual dysfunction with the newer ones (carvedilol, celiprolol) to exert a less pronounced negative effect^[21-24]. A luminous exception to the rule, nebivolol, is a newer agent of its class which significantly ameliorates erectile dysfunction through increased nitric oxide generation, an effect consistently demonstrated in recent studies^[25,26]. Diuretics, even on adjunct therapy, constitute another antihypertensive agent negatively associated with sexual function^[27-29]. On the other hand, calcium antagonists and angiotensin converting enzyme inhibitors seem to demonstrate a neutral effect^[30-32]. Interestingly, angiotensin receptor blockers (ARBs) by blocking the vasoconstrictive action of angiotensin II seem to positively affect erectile function and are thus regarded as a first-line treatment in hypertensive patients with erectile dysfunction^[22,25,33-35].

TREATED HYPERTENSIVE PATIENTS

Whereas management of sexual dysfunction in previ-

ously untreated hypertensive patients can be a challenging procedure, confronting the same clinical condition in individuals under antihypertensive regime can be even more demanding. In such cases there will always be a question hovering over physicians head. Is hypertension *per se*, antihypertensive medication or both, the causative factors provoking sexual dysfunction^[15]?

Duration and severity of hypertension are undoubtedly associated with erectile dysfunction. As a result, patients with long-standing (> 5-6 years) and severe hypertension are expected to suffer more frequently from sexual dysfunction, which indeed appears in a more severe form^[36,37].

When antihypertensive medication comes to the fore, certain issues need to be carefully addressed. This is due to the fact that medically induced erectile dysfunction is one of the major reasons for non-adherence and treatment discontinuation, a reality that could have deleterious consequences on patient's cardiovascular profile and health quality in the long term^[38,39].

Like the case of untreated hypertensive patients, evaluation of sexual dysfunction in hypertensive patients under antihypertensive regime, should primarily exclude other concomitant diseases and pharmaceutical agents. Consecutively, a competent physician with advanced communicational skills should try to "discover" medically induced erectile dysfunction since a vast majority of patients being under complex antihypertensive regimes usually attribute the undesirable effect to normal aging thus not relating it to their current medication. Moreover, even physicians seldom report the cases of sexual dysfunction associated with certain medications. When medically induced sexual dysfunction is finally disclosed and a shift in medication is deemed necessary, b-blockers along with diuretics should generally be the first categories to be changed, unless they are deemed absolutely indicated for the individual patient. Ideally, an ARB could constitute the mainstay of therapy in these cases. If sexual dysfunction still persists, then more effective remedies should be elected paving the way for the introduction of phosphodiesterase-5 inhibitors (PDE-5).

PDE-5 inhibitors

Since their introduction in the therapeutic field, more than a decade ago, PDE-5 inhibitors have revolutionized the treatment of sexual dysfunction. By blocking the activity of PDE-5 isoenzyme, localized throughout the smooth muscle cells of the vasculature (genital vessels included), PDE-5 inhibitors increase the levels of cyclic guanosine monophosphate thus exerting vasodilating properties and facilitating penile erection^[40-42]. Due to these properties, sildenafil was the first drug of its class to receive wide acceptance. Its short half-life, food interactions and the associated visual disturbances however, paved the way for the development of newer PDE-5 inhibitors. As such vardenafil with its more rapid onset of action, and tadalafil with its longer half-life and the lack of food interactions or side effects, have offered signifi-

cant alternatives to sildenafil^[43-50].

Due to their vasorelaxing effect, administration of PDE-5 inhibitors in hypertensive individuals was initially confronted with great suspicion. A wealth of clinical data however has proven that PDE-5 inhibitors are associated with few side effects and provoke a small and insignificant reduction in blood pressure with minimal heart rate alterations in both normotensive and hypertensive patients as well. As a matter of fact, they can be safely and effectively administered to hypertensive individuals even when they are already taking multiple antihypertensive agents^[51-56]. The sole exception to the rule is co-administration with organic nitrates, which is an absolute contraindication due to profound and possibly hazardous hypotension effect^[57,58]. Moreover, precaution should be taken when PDE-5 inhibitors are combined with a-blockers where, due to possible orthostatic hypotension effect, lower starting doses should be implemented in the therapeutic regime^[59-62].

Apart from their beneficial effect in erectile dysfunction and their safe profile in antihypertensive medication, PDE-5 inhibitors have even more advantages to demonstrate. Several lines of evidence has proven that patients receiving PDE-5 inhibitors are more likely to initiate an antihypertensive regime and more willing to add a new agent to their existing treatment, a fact that raises significantly patient's adherence and as a matter of fact control of high blood pressure and quality of life^[63,64]. Moreover, a handful of clinical data has demonstrated the considerable vasodilating and anti-proliferative properties of PDE-5 inhibitors in the pulmonary vasculature, establishing them as a first-line treatment in patients with pulmonary arterial hypertension^[65,66]. The same properties have been considered as potentially responsible for improving microcirculation in patients with secondary Raynaud phenomenon and ameliorating cardiopulmonary exercise performance in patients with heart failure^[67,68]. In addition, the therapeutic implementation of PDE-5 inhibitors has expanded in the field of benign prostate hyperplasia-lower urinary tract symptoms (BPH-LUTS). The common pathophysiologic substrate between erectile dysfunction and BPH-LUTS has rendered PDE-5 inhibitors an effective treatment which significantly improves measures of both conditions while at the same time exhibits high efficacy and safety. The beneficial effect is much more pronounced when taking into consideration the fact that a-blockers, the mainstay of therapy for benign prostate hyperplasia frequently provoke sexual side effects, erectile dysfunction included^[69].

Management beyond PDE-5 inhibitors

Despite remarkable therapeutic efforts, it is evident that a relative proportion of patients with erectile dysfunction will fail to respond to oral pharmacotherapy including PDE-5 inhibitors. The management of non-responders calls for second and third-line treatment implementation.

Surgical implantation of a penile prosthesis, either the inflatable (2- and 3-piece) or the malleable device, is a

feasible technique that offers a third-line treatment and a more permanent solution to the problem of erectile dysfunction. Interestingly, prosthesis implantation receives a significantly high satisfaction rate as evidenced by the proportionate scores in sexual satisfaction scales. Mechanical failure and infection are the two major disadvantages of those prosthetic implants however, their great efficacy, safety and satisfaction rate in general render them an attractive solution when conservative treatment fails^[70-74].

CARDIOVASCULAR RISK PREDICTION

One of the most interesting aspects considering the properties of sexual dysfunction is that, during the last decades, it transformed from being a reliable quality of life index into a significant CV risk predictor.

Towards this direction, several sufficiently powered studies have demonstrated a higher incidence of erectile dysfunction in patients with coronary artery disease, either asymptomatic or overt. At the same time, patients with erectile dysfunction are more prone to have established coronary artery stenosis of more than 50% and consequently evident CV disease^[75]. This is in conformity with the “artery size hypothesis” according to which smaller arteries (*e.g.*, penile arteries) are the first to undergo a vascular lesion prior to the larger ones (*e.g.*, coronary arteries). Moreover, in such patients erectile dysfunction is connected to the number of occluded vessels and more interestingly occurs over three years before coronary artery disease becomes apparent^[76-80].

Several other facts support the close relationship between sexual dysfunction and CV disease. Endothelial dysfunction mediated by decreased nitric-oxide bioavailability as well as atherosclerotic lesions constitute a common pathophysiologic substrate affecting both CV disease and erectile dysfunction, a disease considered to be primarily of vascular origin^[76,80-82]. Several traditional CV risk factors (diabetes mellitus, hypertension, dyslipidemia, and smoking) are frequently found in individuals with erectile dysfunction, conferring a detrimental cardiovascular burden to them. More interestingly, the increased cardiovascular risk observed in those patients is independent of the aforementioned CV risk factors^[81-88].

A recent systematic review and meta-analysis of relevant studies in this field confirmed that erectile dysfunction is associated with increased risk of CV events and all-cause mortality^[89]. The pooled relative risks were 1.44 (95%CI: 1.27-1.63) for total CV events, 1.19 (95%CI: 0.97-1.46) for CV mortality, 1.62 (95%CI: 1.34-1.96) for myocardial infarction, 1.39 (95%CI: 1.23-1.57) for cerebrovascular events, and 1.25 (95%CI: 1.12-1.39) for all-cause mortality, for men with *vs* without erectile dysfunction. Of note, the relative risk was higher in intermediate-compared with high- or low-CV-risk populations and with younger age, with obvious clinical implications. Interestingly, the relative risks were higher when erectile dysfunction was diagnosed with the use of a questionnaire compared with a single question (RR =

1.61; 95%CI: 1.38-1.86 *vs* RR = 1.27; 95%CI: 1.18-1.37, respectively; *P* = 0.006).

Since erectile dysfunction presents such an intimate relationship with CV parameters, it is easily deduced that it could constitute a powerful tool for detecting asymptomatic CV disease. Consequently, recognition of sexual dysfunction in a hypertensive individual should prompt further diagnostic procedures and therapeutic interventions in order to disclose its silent cardiovascular risk and improve patient's quality of life and life expectancy.

SEXUAL ACTIVITY IN PATIENTS WITH CV DISEASE

Considering the fact that CV disease presents with higher incidence in patients with erectile dysfunction while at the same time sexual activity by itself poses potential CV risks, the appropriate management of those complex conditions is of utmost importance. Accordingly, the working group of the third Princeton Consensus Conference developed practical guidelines and a simplified algorithm in order to manage sexual dysfunction and sexual activity implementation issues in patients with different levels of CV risk, including hypertensive patients^[90].

In particular, patients are classified into three categories (low, intermediate, high) depending on their CV risk profile. Individuals with controlled hypertension belong to the low-risk group where sexual dysfunction can be safely managed with the approved medical therapies regardless of the number or class (with the exception of β -blockers and diuretics) of agents of the patient's antihypertensive regime. Moreover, patients of this group can safely initiate or reinstitute sexual activity without any need for additional cardiovascular evaluation.

On the contrary, patients with uncontrolled hypertension (poorly controlled, untreated, accelerated or malignant) belong to the high risk group where both treatment of sexual dysfunction and sexual activity resumption must be deferred until a thorough and specialized evaluation and stabilization has primarily been made.

Erectile dysfunction usually precedes cardiovascular events by 3 to 5 years. Therefore, sexual function should be incorporated into cardiovascular disease risk assessment for all men. Recently, algorithms for the management of patients with erectile dysfunction according to the risk for sexual activity and future cardiovascular events were proposed^[91]. A comprehensive approach to cardiovascular risk reduction (comprising of both lifestyle changes and pharmacological treatment) will result in significant benefits on overall vascular health, including sexual function. Proper sexual counselling will exert beneficial effects on the quality of life of hypertensive patients with erectile dysfunction and will improve adherence to antihypertensive drug therapy^[91].

CONCLUSION

The prevalence of erectile dysfunction is approximately

2-fold higher in hypertensive patients compared to normotensive individuals. However, erectile dysfunction remains under-reported, under-recognized, and under-treated in hypertensive patients. Hypertension *per se* and antihypertensive drug therapy may contribute to the development of erectile dysfunction in patients with arterial hypertension. The management of erectile dysfunction in hypertensive patients is tricky and should take into account the different effects of antihypertensive drug categories on erectile function. Lifestyle modification should be the mainstay of treating erectile dysfunction in patients with untreated hypertension. Switching antihypertensive therapy should be considered in treated hypertensive patients, unless administered drugs are absolutely indicated for the individual patient. Otherwise, PDE-5 inhibitors should be used, since they are both effective and safe in hypertensive patients. Finally, erectile dysfunction offers the opportunity to recognize asymptomatic cardiovascular disease and better characterize the relevant risk with obvious benefits for cardiovascular disease prevention.

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WJC 6th Anniversary Special Issues (3): Cardiomyopathy

Multimodality imaging in apical hypertrophic cardiomyopathy

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Abstract

Apical hypertrophic cardiomyopathy (AHCM) is a relatively rare morphologic variant of HCM in which the hypertrophy of myocardium is localized to the left ventricular apex. Symptoms of AHCM might vary from none to others mimic coronary artery disease including acute coronary syndrome, thus resulting in inappropriate hospitalization. Transthoracic echocardiography is the first-line imaging technique for the diagnosis of hypertrophic cardiomyopathies. However, when the hypertrophy of the myocardium is localized in the ventricular apex might results in missed diagnosis. Aim of this paper is to review the different imaging techniques used for the diagnosis of AHCM and their role in the detection and comprehension of this uncommon disease.

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Key words: Apical hypertrophic cardiomyopathy; Imaging techniques; Cardiac magnetic resonance; Transthoracic echocardiography; Multidetector computed tomography

Core tip: Apical hypertrophic cardiomyopathy (AHCM) is a relatively rare morphologic variant of HCM in which the hypertrophy of myocardium is localized to the left ventricular apex. Aim of this paper is to review the dif-

INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a genetic disorder caused by mutations in one or more of the genes encoding protein components of the cardiac sarcomere and transmitted with an autosomal dominant trait and variable penetrance^[1,2]. The variability of these mutations leads to different morphological features of the pathology and influences patient prognosis^[3,4].

Apical HCM (AHCM) is a relatively rare morphologic variant of HCM in which the hypertrophy of the myocardium is mainly localized to the left ventricular (LV) apex without the typical septal predominance, which characterize hypertrophic obstructive cardiomyopathy. A sarcomere protein gene defects have been found to be present from 13% to 30% of these patients^[5]. It was first described in Japanese patients with precordial deep T wave inversions (referred to as giant T wave inversions) in 1976^[6,7]. This condition is frequent in Asian population accounting for almost 25% of Japanese patients with HCM while its prevalence dramatically decrease in Caucasian patients to 1%-3%^[8-10]. Male gender is the most frequently affected in the Japanese population but this gender difference has not been as relevant outside Japan^[11]. Differences between the “pure” Japanese form of AHCM (hypertrophy of only the apical segments) and the non-Japanese form are reported. AHCM in Caucasian patients presents hypertrophy extended to the middle

Table 1 Comparison of different imaging techniques

	Echocardiography	SPECT	Angiography	MDCT	CMR
LV morphology (dimensions, wall thickness)	++	-	+	++	+++
Global and regional LV function	++	+	+	++	+++
LV filling pressure	++	+	+++	+	++
Radiation	-	+	+	+	-
Ischemia/CAD	+	++	+++	++	++
Tissue characterisation	+	-	-	-	+++
Cost	-	+++	+++	++	++

SPECT: Single photon emission computed tomography; MDCT: Multidetector computed tomography; CMR: Cardiovascular magnetic resonance; LV: Left ventricular; CAD: Coronary artery disease.

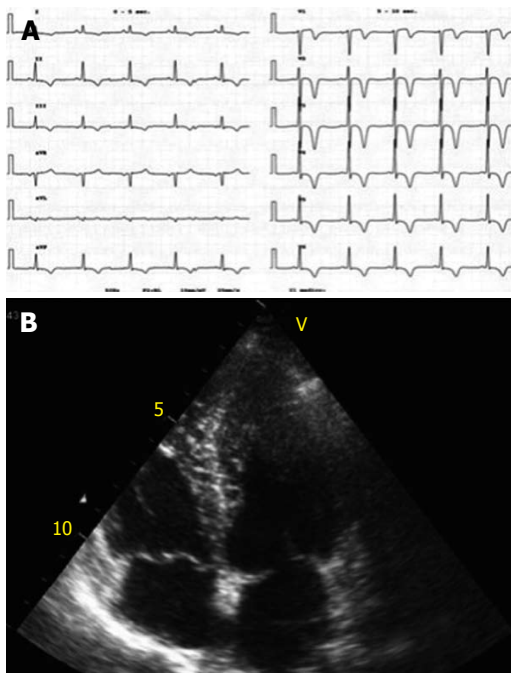


Figure 1 On transthoracic echocardiography, apical hypertrophic cardiomyopathy is defined as an absolute apical thickness of more than 15 mm with a ratio of apical to basal left ventricular wall thickness of more than 1.3. A: 12-lead electrocardiogram with increased in QRS voltage and deep T-wave inversion in the precordial leads; B: Transthoracic echocardiography 4-chambers view showing asymmetrical left ventricular apical thickening with a spade shaped left ventricle configuration.

left ventricle's segment segments ("mixed form"), with a worsened prognosis. These findings suggest a variability in the phenotypic expression of AHCM between countries and races with a possible additional role of environmental factors^[12,13].

AHCM has a relatively benign prognosis in terms of cardiovascular mortality ranging around 0.1% in "pure" forms. However, one-third of the patients may experience unfavourable clinical events and life treating complications: diastolic dysfunction, myocardial infarction, left atrial enlargement with subsequent atrial fibrillation, apical aneurysm and thrombi with ventricular arrhythmias^[10,12]. Moreover, progression into apical aneurysm or mid-ventricular obstruction is a variant and unfavourable feature of the disease. Symptoms might vary from none to others including chest pain in absence of angiographi-

cally proven coronary stenosis, palpitations, dyspnea, fatigue or syncope^[14]. ECG pattern found in up to 90% of cases, include giant negative T waves at rest with transient normalization on exertion. Transthoracic echocardiography is currently the standard diagnostic tool for hypertrophic cardiomyopathies, however its diagnostic accuracy for identification of hypertrophy confined to the LV apex is limited.

Aim of this paper is to briefly review the different imaging techniques in the diagnosis of AHCM and their potential role in expanding our knowledge of this uncommon disease (Table 1).

ECHOCARDIOGRAPHY

Transthoracic echocardiography (TTE) is the first line imaging exam in patient with suspected AHCM because of its widespread availability and low-cost. On TTE, AHCM is defined as an absolute apical thickness of more than 15 mm with a ratio of apical to basal LV wall thickness of more than 1.3 (Figure 1). According to patterns of hypertrophy, two morphologically distinct phenotypes have been described: pure AHCM where the hypertrophy is limited to the apical segments and mixed AHCM with hypertrophy extending to the mid-ventricular level, sparing the basal segments^[15]. Morphological subtypes have been found to be predictors of different prognosis and clinical manifestations^[16]. Tissue Doppler technique enables to document a lowered coronary flow reserve capacity of penetrating intramyocardial coronary arteries^[17]. However, because of technical artefacts and variability of imaging quality, TTE might results in poor detection of endocardial border thus resulting in misleading diagnosis^[18]. Patients with AHCM might develop apical aneurysms and clots mimicking other conditions such as cardiac tumor, isolated ventricular non-compaction, endomyocardial fibrosis, *etc.* The use of microbubbles contrast agent may improve diagnostic sensitivity^[19-23].

Newer Doppler-based techniques have been successfully applied in the diagnosis of AHCM. Reddy *et al*^[24] described paradoxical apical longitudinal strain (systolic lengthening) in two patients with AHCM despite an apparently normal apical wall motion on conventional TTE. Abecasis *et al*^[25] using velocity vector imaging tissue characterization study found abnormal regional velocities and

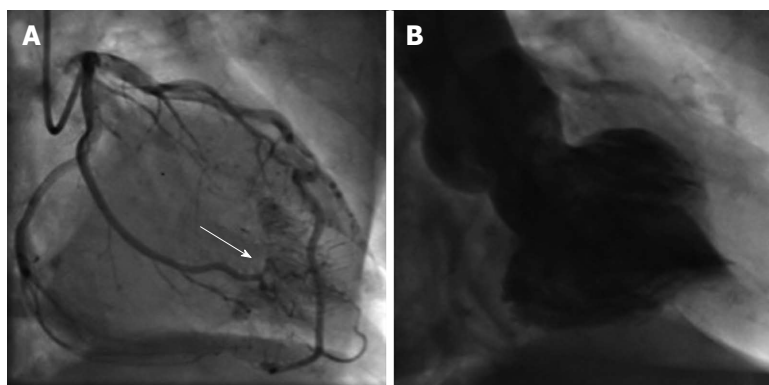


Figure 2 Angiography pictures. A: Coronary angiography showing normal epicardial coronary arteries. Please note the presence of multiple coronary artery-left ventricular microfistulae (white arrow); B: Left ventricular angiography showing the characteristic diastolic “ace-of-spade” sign.

deformation parameters, particularly concerning base to apex longitudinal strain gradient, that could be related to the abnormal tissue hypertrophy extending beyond the more evident apical hypertrophic segments.

Multipane transoesophageal echocardiography enables a correct visualization and sizing of ventricular segments and has been successfully applied in the diagnosis of AHCM^[26].

SINGLE PHOTON EMISSION COMPUTED TOMOGRAPHY

Radionuclide scanning has also been used in diagnosis of AHCM. Reports of stress myocardial perfusion images in patients with AHCM have ranged from normal perfusion to reversible and fixed apical perfusion defects, often in the presence of normal epicardial coronary arteries^[27]. The unbalanced wall thickness-to-vascular supply ratio leads to a relative apical ischemia^[28,29]. Myocardial ischemic chest pain in the absence of coronary artery disease (CAD) has been related to limited coronary flow reserve in patients with asymmetric septal an apical hypertrophy^[29-32]. Morishita *et al*^[33] have also described increased uptake of Tc-99 m tetrofosmin in the apical segment on resting Single Photon Emission Computed Tomography (SPECT) polar maps in a subgroup of patients with AHCM. AHCM increased apical tracer uptake on resting Tl-201 planar and SPECT imaging has been previously reported^[34]. Ward *et al*^[35] showed a newly “Solar Polar” map pattern at rest. This “Solar Polar” map pattern on resting Tl-201 volume-weighted polar maps, sees an intensely bright spot of counts in the apical segment surrounded by a circumferential ring of decreasing counts. This study is the first describing the typical findings on dual-isotope rest and stress SPECT perfusion images and volume-weighted polar maps in non-Japanese patients with AHCM. Three different patterns characteristic of AHCM were identified^[36]: an increased apical tracer uptake, a spade-like configuration of the LV chamber and the “Solar map” in 75% of patients; however no difference in apical thickness and magnitude of T-wave negativity between patients with normal SPECT and typical

pattern were observed. Interstitial fibrosis that prevented the increased apical tracer uptake is the possible explanation for a normal SPECT study in patients with AHCM.

ANGIOGRAPHY

ECG changes and symptoms associated with AHCM often mimic acute coronary syndromes. Moreover elevated troponine serum levels reported in patients with AHCM and chest pain usually encourage physicians to perform invasive testing. Coronary angiography allows to exclude significant epicardial coronary lesions and enables detection of the associated congenital coronary artery anomalies, myocardial bridge or multiple coronary-LV fistulae^[37]. Evaluation of the LV cavity can show the characteristic spade-like configuration of the left ventricle in end-diastole, with obliteration of the apical cavity in end-systole due to the vigour contraction of the hypertrophied myocardium^[7] (Figure 2). Caucasian patients tend to have less localized involvement of the distal apex resulting in a lower frequency of the pathognomonic sign of “ace-of-spade” on the left ventriculography^[13].

MULTIDETECTOR COMPUTED TOMOGRAPHY

Coronary multidetector computed tomography (MDCT) is an high sensitive (91%-99%) and specific (74%-96%) technique in detecting significant coronary stenosis^[38-40]. Major international guidelines currently indicate coronary MDCT for patients at a low to intermediate risk of CAD^[41] and his adoption in the emergency room might facilitate early triage of patients presenting chest pain^[42-44].

MDCT has also emerged as a novel technique for evaluating cardiac morphology and function. Initial concern with MDCT examination with radiation exposure have been overcome by novel technologies using dose-saving strategies^[45,46]. Due to its high spatial resolution, MDCT can offer cardiac anatomical and functional information and a high quality non-invasive coronary evaluation^[47-50]. It also enables accurate delineation of the apical endocardial border and dynamic evaluations of myocar-

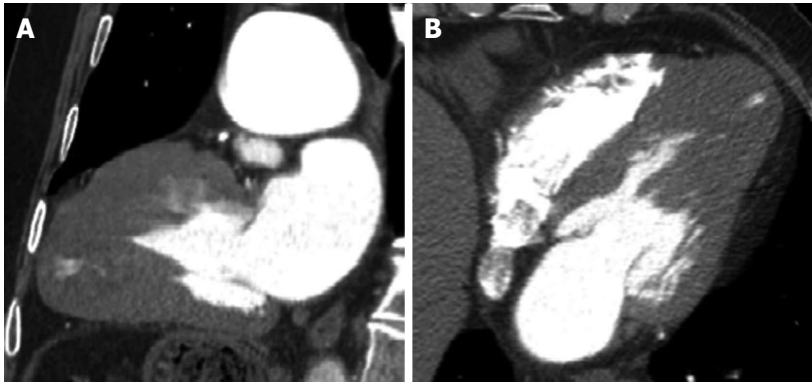


Figure 3 Multidetector computed tomography imaging: Long axis view (A) and axial scans at the level of the left ventricle (B) showing apical hypertrophy with cavity obliteration and a sequestered small left ventricle cavity.

dial thickness, global and regional LV functions^[51]. Multi-planar reconstructions along major cardiac axis allow to measure myocardial thickness on short-axis view in the end-diastolic phase while the apex can be evaluated in long axis planes (Figure 3). Knickelbine *et al.*^[52] have found nonatherosclerotic-related cardiovascular abnormalities judged to be of potential clinical relevance in 4.4% of 4543 patients with suspected atherosclerotic CAD undergoing to 64-slice MDCT. In 50 of these patients (1.1%) the abnormality was previously unrecognized. The most common abnormalities were: congenital coronary artery anomalies (38%), ascending aortic aneurysms > 45 mm (22%), hypertrophic cardiomyopathy with apical LV wall thickening (14%), valvular heart diseases (8%), congenital heart diseases including ventricular septal defect (6%), pulmonary embolus (6%), LV noncompaction, left atrial myxoma, and LV apical aneurysm (2%). Chen *et al.*^[53] have performed MDCT in 14 patients with known diagnosis of AHCM. Left ventricle shapes reconstructions of MDCT were similar to angiography, with “ace-of-spades” configurations, apical sequestrations and apical aneurysm. Furthermore, MDCT was able to detect two cases of significant coronary stenosis and 7 patients with myocardial bridges.

CARDIOVASCULAR MAGNETIC RESONANCE

In the last few years cardiovascular magnetic resonance (CMR) has emerged as a useful and accurate imaging technique for diagnosis of HCM. Both European and American Cardiology Society indicated CMR as first choice exam or at least equivalent to other diagnostic methods in the approach of several cardiomyopathies, including HCM^[54,55].

The excellence of CMR in analyse anatomy and function has increased the sensitivity and specificity of the diagnosis of HCM^[56]. A comparative study of TTE and CMR among HCM subjects demonstrated the greater accuracy of CMR identifying different patterns of hypertrophy. Among subjects with confined hypertrophy in anterolateral wall, echocardiography underestimates wall

thickness and poorly evaluates the apical segments in up to 40%^[57-59]. AHCM may mimic other pathological conditions such as coronary artery disease, myocardial tumor, ventricular aneurysm, ventricular non-compaction or endomyocardial fibrosis and CMR can be useful in differential diagnosis. CMR provides a more accurate assessment of LV apical hypertrophy allowing detection of HCM related complications and wall motion abnormalities (Figure 4). Tsukamoto *et al.*^[60] using CMR-tagging showed systolic outward motion of the LV apical wall in AHCM patients. LV apical aneurysms have been reported in up to 2% of all patients with HCM, with a rate of related adverse events of 10.5% per year, considerably higher with respect to HCM without aneurysm^[61]. Notably, a higher incidence of apical aneurysms, ranging from 10% to 20%^[62,63], has been reported in AHCM. In a case series, Fattori *et al.*^[64] showed that TTE was able to detect only 1 of the 4 cases of AHCM related apical aneurysms, suggesting the use of CMR in all patients affected by AHCM in order to confirm the diagnosis and to ascertain the presence of aneurysms. Indeed, the presence of an apical aneurysm, especially if associated with the detection of ventricular tachyarrhythmias, could support the decision to implant a cardioverter-defibrillator.

CMR appears to be more sensitive than other imaging techniques in detecting infarct areas and ischemia, identifying even subendocardial infarction with late gadolinium-enhanced (LGE)^[65,66]. LGE-CMR has been used to visualize myocardial interstitial abnormalities in patients with different forms of cardiomyopathies, including non-ischemic forms^[67,68]. LGE has been found to be present in a high proportion of patients with HCM and has been associated with a higher incidence of ventricular tachycarrythmias and risk of sudden death^[69,70]. In patients with apical hypertrophic cardiomyopathy, the incidence of LGE seems to be less common with respect to other form of HCMP, but it is similarly associated to a worse prognosis. In the largest available series of AHCM patients imaged with magnetic resonance imaging, LGE was reported only in 40% of cases and limited to the hypertrophic apical segments^[71]. However, others studies showed that LGE was not limited to the hypertrophic

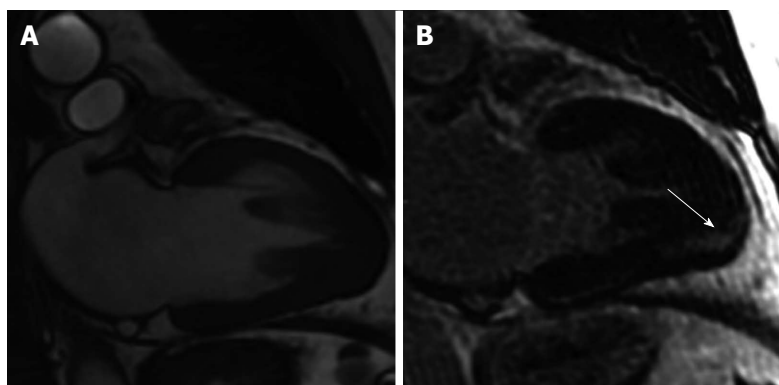


Figure 4 Cardiovascular magnetic resonance imaging. Long axis view (A) of the left ventricle showing apical regional hypertrophy; long axis view 10 min after Gadolinium injection; B: An abnormal hyper-enhancement of the apical segment is visible (white arrow).

apical segments but also present in the midventricular and basal segments of interventricular septum, potential expression of myocardial damage preceding the abnormal hypertrophy. LGE-CMR should be applied for longitudinal follow-up studies to detect development and progression of AHCM related fibrotic tissue formations highlighting the subsets of patients associated with worse prognosis^[72].

CONCLUSION

The correct diagnosis of AHCM is of major importance. Multimodality imaging is essential in increasing the detection of AHCM, yielding larger study populations. In particular, CMR showed an excellent accuracy in identifying the abnormal LV hypertrophy. With late gadolinium enhancement, CMR is able to *in vivo* detect abnormal myocardial structure allowing a more accurate risk stratification.

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WJC 6th Anniversary Special Issues (5): Myocardial infarction

Thrombus aspiration in acute myocardial infarction: Rationale and indication

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Abstract

Reperfusion of myocardial tissue is the main goal of primary percutaneous coronary intervention (PPCI) with stent implantation in the treatment of acute ST-segment elevation myocardial infarction (STEMI). Although PPCI has contributed to a dramatic reduction in cardiovascular mortality over three decades, normal myocardial perfusion is not restored in approximately one-third of these patients. Several mechanisms may contribute to myocardial reperfusion failure, in particular distal embolization of the thrombus and plaque fragments. In fact, this is a possible complication during PPCI, resulting in microvascular obstruction and no-reflow phenomenon. The presence of a visible thrombus at the time of PPCI in patients with STEMI is associated with poor procedural and clinical outcomes. Aspiration thrombectomy during PPCI has been proposed to prevent embolization in order to improve these outcomes. In fact, the most recent guidelines suggest the routine use of manual aspiration thrombectomy during PPCI (class II a) to reduce the risk of distal embolization. Even though numerous international studies have been reported, there are conflicting results on the clinical impact of aspiration throm-

bectomy during PPCI. In particular, data on long-term clinical outcomes are still inconsistent. In this review, we have carefully analyzed literature data on thrombectomy during PPCI, taking into account the most recent studies and meta-analyses.

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Key words: Thrombus aspiration; Thrombectomy; Myocardial reperfusion; Myocardial infarction; No-reflow

Core tip: Distal coronary embolization occurs predominantly at the time of the initial balloon or stent inflation, so thrombus burden reduction by thrombectomy devices before percutaneous coronary intervention may decrease the dangerous phenomenon of no-reflow. Manual aspiration catheters are the most commonly used devices. Several randomized trials have demonstrated the efficacy and safety of pretreatment with manual thrombectomy during primary percutaneous coronary intervention. There are some unanswered questions about thrombus aspiration, including whether there is truly a mortality benefit, which subgroups may or may not benefit from aspiration, and whether patients with a large thrombus burden are better treated with mechanical thrombectomy.

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INTRODUCTION

The final objective of primary percutaneous coronary intervention (PPCI) is successful myocardial reperfusion^[1]. Apart from restoration of flow in the epicardial coronary

artery, the importance of cardiac muscle microcirculation has been emphasized^[2,3]. Myocardial reperfusion failure has been associated with larger infarct size, increased predisposition to ventricular arrhythmias, heart failure, cardiogenic shock, recurrent myocardial infarction, and cardiac death^[4,5].

Different mechanisms are responsible for microvascular injury after PPCI, such as local formation of a thrombus, generation of oxygen-free radicals, myocyte calcium overload, cellular and interstitial edema, endothelial dysfunction, vasoconstriction, and inflammation. However, distal embolization seems to play a pivotal role, and thrombus burden is a predictor of the no-reflow phenomenon and an independent predictor of adverse outcomes^[6-10].

Distal coronary embolization occurs predominantly at the time of initial balloon or stent inflation, so thrombus burden reduction by thrombectomy devices before balloon/stent inflation may decrease the dangerous phenomenon of no-reflow^[11]. Manual aspiration catheters are the most commonly used devices because they are easy and safe to use, even in the elderly^[12], and are relatively inexpensive compared with rheolytic thrombectomy^[13]. Moreover, myocardial salvage is measured and studied in trials through different parameters: angiographic [thrombolysis in myocardial infarction (TIMI) and myocardial blush grade (MBG)], electrocardiographic [ST-segment resolution (STR)], functional (reduction of infarct size) and clinical (enhanced survival free from heart failure events)^[14,15]. Several randomized trials have demonstrated the efficacy and safety of pretreatment with manual thrombectomy during PPCI. Most of the studies in the literature, including meta-analyses, randomized trials or registries, conclude that thrombectomy improves the parameters of myocardial reperfusion, with a rapid and effective STR^[16]. The Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction (TAPAS) Trial, the impact of thrombectomy with EXPort catheter in Infarct-Related Artery during Primary Percutaneous Coronary Intervention (EXPIRA) Trial and some meta-analyses found that aspiration thrombectomy during ST-segment elevation myocardial infarction (STEMI) improves myocardial reperfusion and procedural outcomes, reducing no-reflow, mortality and distal embolization^[17-19]. There are some unanswered questions about thrombus aspiration including whether there is truly a mortality benefit^[20], which subgroups may and may not benefit from aspiration, and whether patients with large thrombus burden are better treated with mechanical thrombectomy.

RATIONALE AND INDICATION

There are many ways to treat the coronary thrombus burden at the time of PPCI: pharmacologic strategies (typically glycoprotein II b/IIIa platelet inhibitors), embolic protection devices (filters and distal balloon occlusion with aspiration), mechanical thrombectomy, and manual

or aspiration thrombectomy devices. This paper reviews the role of manual thrombectomy in patients with STEMI. The evidence supporting the benefit of aspiration thrombectomy on surrogate outcomes (TIMI flow, MBG and STR) and angiographic outcomes (distal embolization and no-reflow) is strong and convincing, while the benefit in reduction of mortality is not strong and has limitations^[19-24].

All randomized trials of aspiration thrombectomy have been performed in "all comers" with STEMI, and it is not clear which subgroups may benefit more and which subgroups may not benefit at all. In the EXPIRA Trial, 175 patients with STEMI were randomized to PPCI alone *vs* PPCI with manual thrombectomy and a significant improvement was shown in the primary endpoints of MBG 3 and complete STR. This study was the first to evaluate infarct size by magnetic resonance imaging, and it found that the extent of microvascular obstruction was less in the acute phase with aspiration (1.7 g *vs* 3.7 g, $P = 0.0003$), and an improvement in infarct size at 3 mo was seen with aspiration (17% to 11%, $P = 0.004$) but not in the control group (14% to 13%, $P = \text{NS}$)^[18]. These data are confirmed by the results of the INFUSE-AMI Trial (Intracoronary Abciximab Infusion and Aspiration Thrombectomy in Patients Undergoing Percutaneous Coronary Intervention for Anterior ST-Segment Elevation Myocardial Infarction) in which the group with thrombectomy plus intracoronary abciximab had a better prognosis^[25].

Based on the TAPAS Trial and the above meta-analyses, the American College of Cardiology/American Heart Association Guidelines and the European Society of Cardiology Guidelines have given aspiration thrombectomy a Class IIa (Level of Evidence B) indication in PPCI for STEMI. The committee did not consider the evidence for benefit on clinical outcomes strong enough to warrant a Class I indication^[22].

The literature and clinical practice clearly show that the impact of thrombectomy on all outcomes is linked to multiple factors during STEMI, in particular time from symptom onset to PCI, and infarct-related coronary artery and intracoronary thrombus burden.

Sianos *et al*^[26] have shown that both angiographic and clinical outcomes are poorer in patients with a large thrombus burden (≥ 2 vessel diameters) in a new thrombus classification. A large thrombus burden is associated with a greater frequency of major adverse cardiac events, and is a strong independent predictor of late mortality. Moreover, Napodano *et al*^[27] found that patients with right coronary artery infarcts, long lesions and a high thrombus score had the highest frequency of distal embolization. We might expect these subgroups to benefit most from thrombectomy, but data from the TAPAS trial do not support this. Improvement in MBG with aspiration was no better in patients with right coronary artery (RCA) infarcts *vs* non-RCA infarcts, and was no better in patients with a visible thrombus compared with patients without a visible thrombus. There was a trend for greater

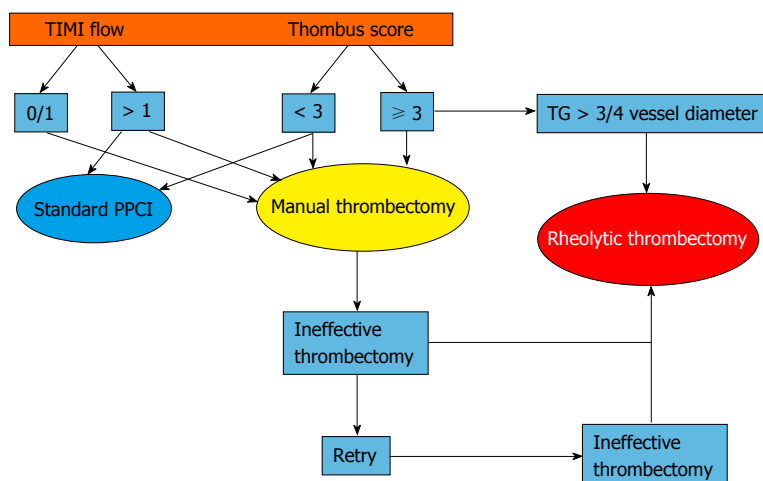


Figure 1 The pathway indicated by the green arrow is recommended during primary percutaneous coronary intervention. PPCI: Primary percutaneous coronary intervention; TIMI: Thrombolysis in myocardial infarction.

benefit in patients with a reperfusion time of less than 3 h, but there were no differential benefits in patients stratified by pre-PCI TIMI flow^[17]. Overall, there are few current studies to support selective use of aspiration thrombectomy in any subgroup of STEMI patients treated with PPCI^[28-30].

Recently, the TASTE Trial (Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia), a randomized study using a platform of a clinical registry, enrolled 7244 STEMI patients who were treated with standard PPCI or manual thrombectomy before PCI. This trial had an ambitious primary endpoint, that is, to reduce 30-d all-cause mortality, and it concluded that routine thrombectomy in PPCI does not reduce this event^[31]. In our opinion, in this study, it was excessive to expect a mortality reduction at 30 d, and would have been more logical to have a primary end-point with a mean follow-up of at least 1 year, as in TAPAS. The TASTE trial design was based on national heart registries and on a secondary randomization that could introduce an initial bias; moreover, there were no reported procedural data such as TIMI flow post-aspiration, MBG or STR. Finally, the frequency of thrombus score greater than 3 was very low (32%) in the total population (54% of patients in the TASTE trial). Instead in the EXPIRA trial, an important inclusion criteria was a higher visible thrombus burden (score ≥ 3) identifying patients at highest risk of coronary distal embolization. Data reported in the literature and guidelines indicate that manual thrombus aspiration should always be considered during PPCI to reduce the risk of distal embolization, in particular in cases of intraluminal thrombosis with a score ≥ 3 .

Aspiration thrombectomy has limited ability to remove a large thrombus and may sometimes be associated with incomplete thrombus removal, no-reflow, and/or distal emboli. There is previous and very recent evidence that mechanical thrombectomy may effectively improve outcomes in patients with a large thrombus burden. Whether mechanical thrombectomy is preferable to aspiration thrombectomy in patients with a large thrombus

burden remains an unanswered question^[32].

CONCLUSION

In our opinion, based on the literature and clinical practice, manual thrombectomy can be used as first approach during PPCI to prevent distal embolization in the case of a visible thrombus burden. As demonstrated in the RET-AMI trial, the new generation manual thrombectomy devices are superior to the first generation tools to remove a greater thrombotic burden, providing higher post-thrombectomy epicardial flow and better post-stenting microvascular reperfusion^[33].

From a “real world point of view”, to perform a good manual thrombectomy, the culprit vessel diameter could be > 2.5 mm with a TIMI flow 0-1 and a visible thrombus (score > 3). The device, however, has to advance delicately over the thrombotic occlusion to perform continuous intracoronary blood suction. In the case of a large thrombus burden, it is now possible to use a 7 Fr intracoronary manual thrombectomy device or rheolytic tools with greater suction force (Figure 1). In conclusion, in the treatment of acute myocardial infarction, thrombectomy should be considered as one of the most important therapeutic tools, with the purpose of cardioprotection and myocardial salvage.

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Drug-eluting stents and acute myocardial infarction: A lethal combination or friends?

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Abstract

Primary percutaneous coronary intervention is the preferred reperfusion strategy for patients presenting with ST-segment elevation myocardial infarction (STEMI). First generation drug-eluting stents (DES), (sirolimus drug-eluting stents and paclitaxel drug-eluting stents), reduce the risk of restenosis and target vessel revascularization compared to bare metal stents. However, stent thrombosis emerged as a major safety concern with first generation DES. In response to these safety issues, second generation DES were developed with different drugs, improved stent platforms and more biocompatible durable or bioabsorbable polymeric coating. This article presents an overview of safety and efficacy of the first and second generation DES in STEMI.

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Key words: ST-segment elevation myocardial infarction; Drug-eluting stents; Stent thrombosis; Sirolimus drug-eluting; Paclitaxel drug-eluting stents; Zotarolimus-eluting stents; Zotarolimus-eluting stents; Bioresorbable vascular scaffold

Core tip: Primary percutaneous coronary intervention is the preferred reperfusion strategy for patients present-

ing with ST-segment elevation myocardial infarction (STEMI). First-generation drug-eluting stents (DES) reduce restenosis and target vessel revascularization compared to bare metal stents at the expense of an increased stent thrombosis rate. Recent improvements in second-generation DES have overcome these safety concerns. This article presents an overview of safety and efficacy of the DES in STEMI.

Otsuki S, Sabaté M. Drug-eluting stents and acute myocardial infarction: A lethal combination or friends? *World J Cardiol* 2014; 6(9): 929-938 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v6/i9/929.htm> DOI: <http://dx.doi.org/10.4330/wjc.v6.i9.929>

INTRODUCTION

Primary percutaneous coronary intervention (PCI) has become a well-established reperfusion strategy for patients presenting with acute ST-segment elevation myocardial infarction (STEMI)^[1,2]. In this setting, bare-metal stents (BMS) reduced the risk of recurrent ischemia and restenosis compared to balloon angioplasty^[3]. First-generation drug-eluting stents (DES)-sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES)-were also able to reduce the risk of restenosis and target-vessel revascularization (TVR) compared to BMS in this context^[4,5]. However, stent thrombosis emerged as a major safety concern^[6]. In response, second-generation DES were developed with different drugs, more biocompatible durable polymers or bioabsorbable polymeric coatings, and new stent platforms, including fully bioresorbable vascular scaffolds.

PATHOPHYSIOLOGY OF STEMI

As shown in Figure 1, STEMI is an event related to ath-

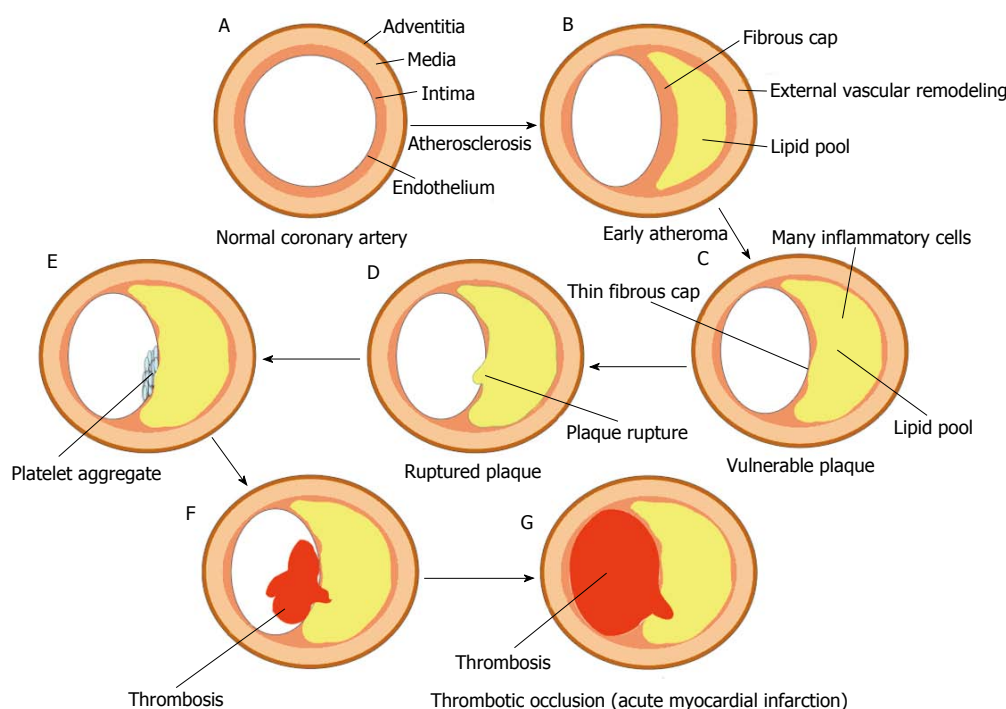


Figure 1 Pathophysiology of ST-segment elevation myocardial infarction. A: Normal coronary artery; B: Coronary artery with early atheroma; C: Vulnerable plaque with thin fibrous cap; D: Ruptured plaque; E: Platelets aggregated to heal the ruptured plaque; F: Protruding thrombus; G: Thrombotic occlusion (acute myocardial infarction).

erosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection that results in intraluminal thrombus in one or more of the coronary arteries, leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis^[7,8]. During the early years after the introduction of coronary stents, it was thought that implanting a metallic device under a thrombotic environment in the acute phase of STEMI could increase the risk of adverse outcome. However, refinement of stent implantation technique and the development of new anti-thrombotic regimen have overcome those initial concerns.

PATHOPHYSIOLOGY OF STENT THROMBOSIS

The pathophysiology of stent thrombosis includes procedure-, stent-, and patient-related factors (Figure 2). The PCI procedure for acute coronary syndrome, including STEMI, is one of the most powerful predictors for stent thrombosis in the vast majority of registries^[9-14] (Figure 3). Late stent malapposition is common in STEMI patients and may eventually provoke stent thrombosis. Late malapposition may be linked to underdeployment of stents at the time of STEMI treatment, due mainly to dissolution of thrombus behind the struts or undersized vessels due to the spastic condition of the coronary arteries in the acute phase of STEMI^[15]. Implanting DES over a necrotic core may also significantly delay healing, due to less neointimal growth and greater inflammation, fibrin deposits, and uncovered struts compared to DES implanted over coronary stable plaques^[16,17].

Currently, patients are categorized as having early or late stent thrombosis. Early stent thrombosis is defined as occurring within 30 d of implantation, and is further categorized as acute (events within 24 h) or subacute (events on day 1-30) thrombosis. Events that occur more than 30 d postimplantation are classified as late stent thrombosis, and those occurring beyond 12 mo as very late stent thrombosis^[18].

Early and late stent thrombosis differ in their pathophysiology and mechanism. Early stent thrombosis is mainly related to one or more procedural characteristics, such as stent underexpansion, incomplete stent apposition, dissection, thrombus, tissue protrusion, and persistent slow flow. It may occur after either BMS or DES implantation.

Late stent thrombosis may result when neointimal healing is delayed, as this can lead to inadequate neointimal coverage and/or to incomplete stent apposition. Evaluation of angiography, optical coherence tomography, and autopsy revealed that first-generation DES are associated with delayed arterial healing due to hypersensitive reactions to polymers that cause chronic inflammation^[9,16]. These phenomena are typically observed more than 1 year after implantation.

SAFETY AND EFFICACY OF FIRST-GENERATION DES IN STEMI

Twelve randomized controlled trials (RCTs) of first-generation DES outcomes in STEMI have been published^[14,5,19-33]. Comparisons were made as follows: BMS

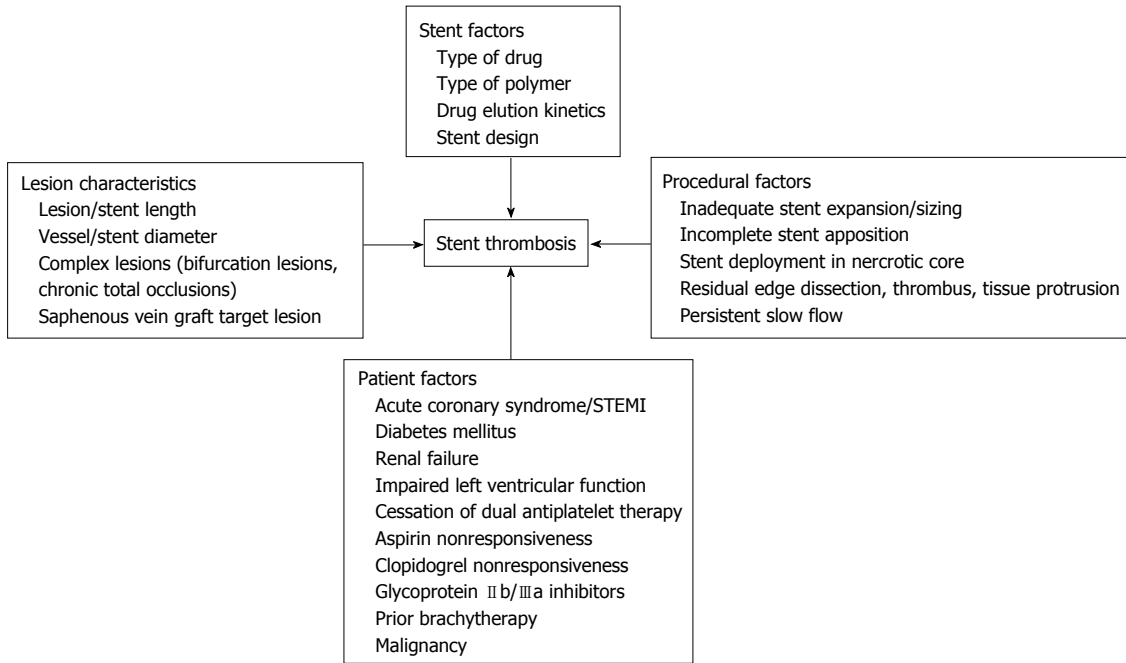


Figure 2 Potential causes of stent thrombosis. STEMI: ST-segment elevation myocardial infarction.

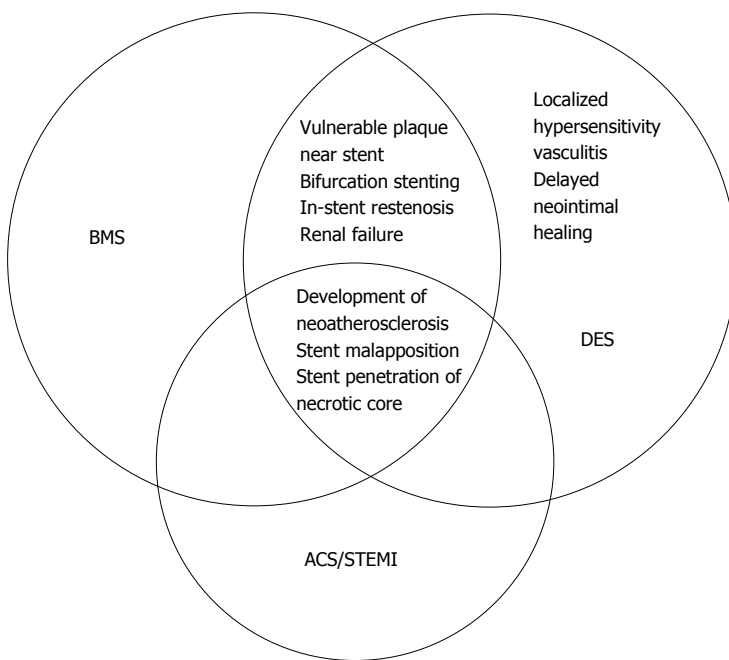


Figure 3 Multifactorial causes of late stent thrombosis. BMS: Bare metal stents; DES: Drug eluting stents; ACS: Acute coronary syndrome; STEMI: ST elevated myocardial infarction.

vs SES, 7 reports; BMS *vs* PES, 5 reports; PES *vs* SES, 2 reports; BMS *vs* SES *vs* PES, 1 report (Table 1).

The TYPHOON study^[4] was the largest RCT to consider SES, enrolling 712 patients to assess the effectiveness and safety of SES *vs* BMS at 1 year. Target-vessel failure was significantly lower in the SES (7.3%) than in the BMS (14.3%) group ($P = 0.004$), driven by a decrease in the rate of TVR (5.6% *vs* 13.4%, respectively; $P < 0.001$). There was no significant difference between the two groups in the rates of mortality (2.3% *vs* 2.2%; $P = 1.00$), repeat myocardial infarction (MI) (1.1% *vs* 1.4%; P

$= 1.00$), or stent thrombosis (3.4% *vs* 3.6%; $P = 1.00$). At 4-year follow-up^[4], freedom from target lesion revascularization was significantly better in the SES group, compared to BMS (92.4% *vs* 85.1%; $P = 0.002$). However, no differences were observed, respectively, in freedom from cardiac death (97.6% *vs* 95.9%; $P = 0.37$), freedom from repeat MI (94.8% *vs* 95.6%; $P = 0.85$), or definite/probable stent thrombosis (4.4% *vs* 4.8%, $P = 0.83$). Other studies have also reported that SES was superior or non-inferior to BMS in mortality, repeat MI, TVR, and stent thrombosis rates^[20-25,33] (Table 1).

Table 1 Randomized controlled trials of first-generation drug eluting stents in stent thrombosis elevated myocardial infarction

Study, author (Ref.)	Year	Primary endpoint	Design	Randomized ratio	Maximal length of follow-up	Stent comparators (n)	Results of the primary endpoint
Pascari <i>et al</i> ^[19]	2003	Death, MI, recurrent ischemia at 1 yr	Single center	1:1	1 yr	BMS/SES 65 (33/32)	No significant differences between stents
TYPHOON ^[4]	2006	TVF at 1 yr	Multicenter, superiority	1:1	4 yr	BMS/SES 712 (355/357)	SES superior to BMS
STRATEGY ^[20]	2007	Death, MI, stroke, binary restenosis at 8 mo	2-center, superiority	1:1	2 yr	BMS/SES 175 (87/88)	SES superior to BMS
SFESAMI ^[21,22]	2007	Binary restenosis at 1 yr	Single-center, superiority	1:1	5 yr	BMS/SES 320 (160/160)	SES superior to BMS
Díaz de la Llera <i>et al</i> ^[23]	2007	Death, MI, TLR at 1 yr	Single center, superiority	1:1	1 yr	BMS/SES 114 (54/60)	SES superior to BMS
MISSION ^[24]	2008	In-segment late luminal loss at 9 mo	Single center, noninferiority	1:1	5 yr	BMS/SES 310 (152/158)	SES superior to BMS
MULTISTRATEGY ^[25]	2008	Death, MI, clinically driven TVR at 8 mo	Multicenter, superiority	1:1	3 yr	BMS/SES 744 (372/372)	SES superior to BMS
HAAMU-STENT ^[26]	2006	Death, MI, late lumen loss, TVR at 1 yr	Single center, superiority	1:1	1 yr	BMS/PES 164 (82/82)	PES superior to BMS
SELECTION ^[27]	2007	Neointimal proliferation by IVUS at 7 mo	Single-center, superiority	1:1	7 mo	BMS/PES 76 (39/37)	PES superior to BMS
PASSION ^[28]	2008	Cardiac death, MI, TLR at 2 yr	2-center, superiority	1:1	5 yr	BMS/PES 619 (310/309)	Superiority not demonstrated
HORIZONS-AMI ^[5,29]	2009	Death, MI, stroke, or ST at 1 yr	Multicenter, superiority (TLR) Noninferiority (Death, MI, stroke, ST)	3:1	3 yr	BMS/PES 3006 (2257/749)	PES superior for TLR and noninferior for clinical endpoints
GRACIA-3 ^[30]	2010	In-segment binary restenosis, myocardial flow at 1 yr	Multicenter, noninferiority	1:1	1 yr	BMS/PES 419 (210/209)	BMS noninferior to PES
PROSIT ^[31]	2008	Death, MI, TVR, ST at 1 yr	Multicenter, superiority	1:1	3 yr	PES/SES 308 (154/154)	Superiority not demonstrated
Juwana <i>et al</i> ^[32]	2009	Late lumen loss at 9 mo	Single center, superiority	1:1	1 yr	PES/SES 397 (196/201)	SES superior to PES
PASEO ^[33]	2009	TLR at 12 mo	Single-center, superiority	1:1:1	4 yr	BMS/PES/SES 270 (90/90/90)	PES and SES superior to BMS

MI: Myocardial infarction; TLR: Target lesion revascularization; ST: Stent thrombosis; PES: Paclitaxel-eluting stents; SES: Sirolimus-eluting stents; BMS: Bare metal stent stents; TVR: Target vessel revascularization; IVUS: Intra-vascular ultrasound.

With regard to PES, the HORIZONS-AMI study was the largest RCT^[5]. A total of 3006 patients were enrolled in this 12-mo trial to assess the effectiveness and safety of PES *vs* BMS. The PES group had significantly lower 12-mo rates of ischemia-driven target lesion revascularization (4.5% *vs* 7.5%; *P* = 0.002) and TVR (5.8% *vs* 8.7%; *P* = 0.006). There were no significant differences between the PES and BMS groups in 12-mo rates of mortality (3.5% *vs* 3.5%; *P* = 0.98) and stent thrombosis (3.2% *vs* 3.4%; *P* = 0.77). At the 3-year follow-up^[29], the PES group had lower rates of ischemia-driven target lesion revascularization (9.4% *vs* 15.1%; *P* < 0.0001), but did not differ from the BMS group in mortality, repeat MI, stroke, or stent thrombosis rates. Stent thrombosis was high (\geq 4.5%) in both groups. Other studies have also shown that PES was superior or noninferior to BMS in mortality, repeat MI, TVR, and stent thrombosis rates^[26,27,30,33] (Table 1).

Although RCTs did not identify any safety issues with first-generation DES, this topic became a firestorm during the 2006 European Society of Cardiology Annual Meet-

Table 2 Randomized controlled trials of second-generation drug eluting stents in ST elevated myocardial infarction

Study	Year	Primary endpoint	Design	Randomized ratio	Maximal length of follow-up	Stent comparisons (n)	Results of the primary endpoint
ZEST-AMI ^[38]	2009	Death, MI, and ischemia-driven TVR at 1 yr	Multicenter, safety study	1:1:1	1 yr	PES/SES/PC-ZES 328 (110/110/108)	No significant differences between stents
KOMER ^[39]	2011	Cardiac death, MI, ischemia-driven TLR at 1 yr	Multicenter, safety study	1:1:1	18 mo	PES/SES/PC-ZES 611 (202/204/205)	PC-ZES as safe as SES and PES
EXAMINATION ^[40,41]	2011	Death, MI, any revascularization at 1 yr	Multicenter, superiority	1:1	2 yr	CoCr-EES/BMS 1504 (751/747)	CoCr-EES superior to BMS
XAMI ^[42]	2012	Cardiac death, MI, TVR at 1 yr	Multicenter, noninferiority	2:1	1 yr	EES/SES 625 (404/221)	EES noninferior to SES
COMFORTABLE AMI ^[43]	2012	cardiac death, reinfarction, and TLR at 1 yr	Multicenter, superiority	1:1	1 yr	EES/BMS 1161 (575/582)	BES superior to BMS

MI: Myocardial infarction; TLR: Target lesion revascularization; CoCr-EES: Cobalt-chromium everolimus-eluting stents; PC-ZES: Phosphorylcholine polymer based zotarolimus-eluting stent; PES: Paclitaxel-eluting stents; SES: Sirolimus-eluting stents; TVR: Target vessel revascularization; BMS: Bare metal stent stents.

ing, held in Barcelona. Meta-analysis of pooled data showed that first-generation DES increased mortality and repeat MI compared to BMS^[34]. High rates of early and late stent thrombosis after discontinuation of dual antiplatelet agents in patients treated with first-generation DES also raised safety concerns^[35,36]. Pathology studies demonstrated that the durable polymers used in first-generation DES could cause a delay in arterial healing, characterized by persistent fibrin deposits, delayed hypersensitivity reactions, and poor endothelialization of the vessel wall, all of which increased the thrombotic risk^[37].

SAFETY AND EFFICACY OF SECOND-GENERATION DES IN STEMI

Second-generation DES were developed to resolve these issues. Stent design and polymeric coating were improved by the use of biocompatible or bioabsorbable polymers. Two RCTs have been published about zotarolimus-eluting stents (ZES) implantation in STEMI patients^[38,39] (Table 2).

The multicenter, prospectively randomized, ZEST-AMI trial included 328 patients who were randomly assigned to ZES ($n=108$), SES ($n=110$), or PES ($n=110$) groups^[38]. Mortality, MI, and ischemia-driven TVR rates at 12 mo were 11.3%, 8.2%, and 8.2%, respectively ($P=0.834$); there were no differences in mortality, recurrent MI, and ischemia-driven TVR rates. The SES group had 2 acute and 2 subacute cases of stent thrombosis. In the PES group, 3 patients had subacute thrombosis.

The KOMER study was also a multicenter, prospective, single-blind RCT^[39]. The 611 participants were STEMI patients undergoing primary PCI. They were randomized to treatment with ZES ($n=205$), SES ($n=204$), or PES ($n=202$). At 12-mo follow-up, the incidence of cardiac death, MI, or ischemia-driven target lesion revascularization was 5.9% in the ZES group, 3.4% in the SES group, and 5.7% in the PES group, respectively ($P=0.457$). The rate of stent thrombosis was similar in all 3 groups (approximately 2%).

Two RCTs have studied the use of everolimus-eluting stents (EES) implantation in STEMI patients^[40,42]. The EXAMINATION study was a multicenter, prospective, randomized, all-comer, controlled trial. In this trial, 1498 patients were randomly assigned to receive EES ($n=751$) or BMS ($n=747$)^[40]. At 1-year follow-up, target lesion and vessel revascularization were significantly lower in the EES group (2.1% vs 5.0%; $P=0.003$, and 3.7% vs 6.8%; $P=0.0077$). There were no differences between the EES and BMS groups in all-cause (3.5% vs 3.5%, $P=1.00$) or cardiac death (3.2% vs 2.8%, $P=0.76$) or repeat-MI (1.3% vs 2.0%, $P=0.32$). Stent thrombosis rates differed significantly between EES and BMS groups for both “definite” and “definite or probable” diagnoses (0.5% vs 1.9% and 0.9% vs 2.5%, respectively; both $P=0.019$). At the 2-year follow-up, there were significantly fewer target lesion revascularizations in the EES group (2.9% vs 5.6% for BMS; $P=0.009$)^[41]. Composite of all-cause death, any MI, or revascularization did not differ between groups (14.4% vs 17.3%, respectively; $P=0.11$). Definite and probable stent thrombosis rates were significantly lower in the EES group (1.3% vs 2.8%; $P=0.03$).

The XAMI trial randomized 625 patients with acute myocardial infarction (2:1) to receive EES or SES^[42]. Death, nonfatal MI, or any TVR at 1 year was lower at 4.0% for

Table 3 Current polymer-free stents undergoing clinical evaluation

Stent	Study	Platform	Drug	Primary endpoint	Design	Randomized ratio	Stent comparisons (n)	Result
Yukon (Translumina)	ISAR TEST ^[50]	316 L microporous surface	Sirolimus + Probucol	MACE/ST at 1yr	RCT	2:1	Yukon/R-ZES 3002 (2002/1000)	Noninferior
Cre 8 (CID)	NEXT ^[51]	CoCr abluminal reservoirs	Amphilimus	LL at 6 mo	RCT	1:1	Cre 8/PES 323 (162/161)	Superior
BioFreedom DCS (Biosensors)	BioFreedom FIM ^[52]	316 L microstructured surface	Biolimus A9	LL at 12 mo	RCT	1:1:1	Standard dose/low dose Biofreedom/PES 182 (60/62/60)	Noninferior
Vestasync (MIV therapeutics)	VESTASYN II ^[53]	316 L microporous nanofilm Hap	Sirolimus	LL at 4 and 9 mo	RCT	2:1	VESTASync/BMS 75 (50/25)	Superior
Amazonia Pax (Minvasys)	Pax A and Pax B	CoCr nontextured	Paclitaxel	LL at 6 mo	RCT	1:1	PAXA/PES 30 (15/15), PAXB = 100	Noninferior
Yinyi (Liaoning Biomed.Mat)	FREEDOM ^[54]	316 L micropores	Paclitaxel	MACE/ST/TVR	RCT	2:1	Yinyi/SES 1626 (931/449)	Noninferior
Bicare+	BICARE ^[56]	316 L	Sirolimus + Probucol	TVF at 30 d	FIM	-	$n = 32$	TVF = 9.4%, LL 0.14, ISR = 3.2%
Pronova XR (Vascular Concepts)	EURONOVA XR I ^[55]	Co-Cr	Sirolimus	LL at 6 mo	FIM	-	$n = 50$	In-stent LL 0.45
Focus NP (Envision Scientific)	Nano active FIM	316 L nontextured	Sirolimus nanoparticles	LL at 6 mo	FIM	-	$n = 100$	Ongoing
Mitsu (Meril Medical)	-	CoCr ultrathin struts	Merilimus	-	-	-	Planned	-
Hollow-core DFS (Medtronic)	-	CoCr holes and hollow tube	Sirolimus	-	-	-	Planned	-
Nano+ (Lepu medical)	Nano+	Microporous	Sirolimus	OCT evaluation	FIM	-	$n = 45$	Ongoing

MACE: Major adverse cardiac events; ST: Stent thrombosis; RCT: Randomized control trial; LL: Late lumen loss; R-ZES: Resolute zotarolimus-eluting stents; PES: Paclitaxel-eluting stents; BMS: Bare metal stents; SES: Sirolimus-eluting stents; TVR: Target vessel revascularization; TVF: Target vessel failure; ISR: In-stent restenosis; OCT: Optical coherence tomography; FIM: First-in-man trial.

EES vs 7.7% for SES ($P = 0.048$) and 1-year incidence of definite and/or probable stent thrombosis was 1.2% for EES vs 2.7% for SES ($P = 0.21$).

The COMFORTABLE AMI is the only RCT by the use of biolimus-eluting stents (BES) in STEMI patients^[43]. A total of 1161 patients were randomized 1:1 to receive BES ($n = 575$) or BMS ($n = 582$). Major adverse cardiac events at 1 year occurred in 24 patients (4.3%) receiving BES and in 49 patients (8.7%) receiving BMS ($P = 0.004$). The difference was driven by a lower risk of target vessel-related repeat MI [3 (0.5%) vs 15 (2.7%); $P = 0.01$] and ischemia-driven target-lesion revascularization [9 (1.6%) vs 32 (5.7%); $P = 0.001$] in patients receiving BES compared with those receiving BMS. Rates of cardiac death were not significantly different [16 (2.9%) vs 20 (3.5%), $P = 0.53$]. Definite stent thrombosis occurred in 5 patients (0.9%) treated with BES and 12 patients (2.1%, $P = 0.10$) treated with BMS.

Recent meta-analyses also showed that EES were associated with significantly lower rates of stent thrombosis than both BMS and PES at 1-year follow-up. In addition, EES were associated with significantly lower rates of cardiac death or MI compared with PES^[44,45].

Pathological analysis also showed that late and very late stent thrombosis occurred less often in the EES (4%) than in the SES (21%; $P = 0.029$) and PES groups (26%; $P = 0.008$). The percentage of uncovered struts was lower in the EES (media $n = 2.6\%$) than in SES (18.0%; $P < 0.0005$) or PES groups (18.7%; $P < 0.0005$). Furthermore, EES was associated with less inflammation, no hypersensitivity, and less fibrin deposit than both SES and PES^[46].

GLIMPSE INTO THE FUTURE: NEXT-GENERATION STENT PLATFORMS FOR STEMI?

A new, self-apposing stent has been developed to reduce malapposition, which may eventually provoke stent thrombosis. In the APPOSITION II study, optical coherence tomography at 3 d after implantation showed a lower rate of malapposed stent struts in the self-apposing BMS group than in the balloon-expandable group (0.58% *vs* 5.46%, $P = 0.001$)^[47]. In the APPOSITION IV study, patients treated with a self-apposing SES had better apposition ($P = 0.001$) and better coverage at 4-mo follow-up than the balloon-expandable ZES (31.6% *vs* 3.8%; $P = 0.03$)^[48].

The micronet-mesh-covered stent has been developed to prevent distal embolization. In the MASTER study, complete ST-segment resolution was significantly improved in patients treated with micronet-mesh-covered stent, compared with commercially available BMS or SES (57.8% *vs* 44.7%; $P = 0.008$)^[49].

NONPOLYMERIC STENTS IN STEMI

Nonpolymeric stents have been developed to avoid polymer-related delayed neointimal healing and late stent thrombosis, and several have undergone clinical investigation (Table 3). However, most of the clinical data have been gathered in low-risk patients without STEMI^[50-56]. A small study showed that polymer-free PES (PF-PES) were noninferior to polymer-based PES (PB-PES) in patients with STEMI, both in terms of target lesion failure (10.9% PB-SES *vs* 12.0% PF-PES; $P = 0.861$) and definite or probable stent thrombosis (1.8% PB-SES *vs* 2.0% PF-PES; $P = 1.000$) at one year^[57].

BIORESORBABLE SCAFFOLDS IN STEMI

Fully bioresorbable vascular scaffold (BVS) was developed to overcome problems associated with a durable polymer and metallic scaffold. Disappearance of the stent from the treated site might decrease the risk of stent thrombosis. So far, a few studies with short-term follow-up have been published about bioresorbable vascular scaffold in STEMI or acute coronary syndrome^[58-61]. Further studies in a larger number of patients and long-term follow-up are planned.

The ongoing ISAR-absorb MI trial (A Prospective, Randomized Trial of BVS *vs* EES in Patients Undergoing Coronary Stenting for Myocardial Infarction, www.clinicaltrial.gov, NCT01942070) tests the clinical performance of the everolimus-eluting BVS *vs* durable polymer EES in patients undergoing PCI in the setting of acute MI. The primary endpoint is percent diameter stenosis in angiographic follow-up at 6 to 8 mo. Subsequent clinical follow-up will be undertaken up to 5 years.

Another ongoing study is ABSORB STEMI: the TROFI II trial (www.clinicaltrial.gov, NCT01986803), a

prospective, single-blind, noninferiority, European multicenter RCT. The primary endpoint is to assess the neointimal healing score as evaluated by intracoronary optical frequency domain imaging in patients with STEMI and treated with everolimus-eluting BVS at 6 mo follow-up, compared to that of EES. Furthermore, the safety and feasibility of implanting everolimus-eluting BVS in patients with STEMI will be assessed.

CONCLUSION

The second-generation DES significantly reduced TVR compared with BMS, without an increase in mortality, MI, or stent thrombosis rates. In patients with STEMI, the use of second-generation DES appears safer and more efficacious than either BMS or first-generation DES. Results of the ongoing ISAR-absorb trial and ABSORB STEMI: the TROFI II trial will shed light on the potential benefits of the new BVS in the context of STEMI.

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miRNome in myocardial infarction: Future directions and perspective

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Abstract

MicroRNAs (miRNAs), which are small and non-coding RNAs, are genome encoded from viruses to humans. They contribute to various developmental, physiological and pathological processes in living organisms. A huge amount of research results revealed that miRNAs regulate these processes also in the heart. miRNAs may have cell-type-specific or tissue-specific expression patterns or may be expressed ubiquitously. Primary studies of miRNA involvement in hypertrophy, heart failure and myocardial infarction analyzed miRNAs that are enriched in or specific for cardiomyocytes; however, growing evidence suggest that other miRNAs, not cardiac or muscle-specific, play a significant role in cardiovascular disease. Abnormal miRNA regulation has been shown to be involved in cardiac diseases, suggesting that miRNAs might affect cardiac structure and function. In this review, we focus on miRNAs that have been found to contribute to the pathogenesis of myocardial infarction (MI) and the response post-MI and characterized as diagnostic, prognostic and therapeutic targets. The majority of these studies were performed using mouse and rat models of MI, with a focus on the

identification of basic cellular and molecular pathways involved in MI and in the response post-MI. Much research has also been performed on human and animal plasma samples from MI patients to identify miRNAs that are possible prognostic and/or diagnostic targets of MI and other MI-related diseases. A large proportion of research is focused on miRNAs as promising therapeutic targets and biomarkers of drug responses and/or stem cell treatment approaches. However, only a few studies have described miRNA expression in human heart tissue following MI.

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Key words: MicroRNAs; Myocardial infarction; Human; Animal models; Biomarkers and targets

Core tip: MicroRNAs (miRNAs) contribute to various developmental, physiological and pathological processes in the heart. Cardiac diseases show abnormal miRNA regulation. Primary studies of miRNA involvement in cardiac disease analyzed mainly miRNAs that enriched in or specific for cardiomyocytes; however, growing evidence suggests that other cell-type specific or ubiquitously expressed miRNAs are also involved in cardiovascular disease. miRNAs were found to contribute to the pathogenesis of myocardial infarction (MI) and post-MI. The majority of studies focused on miRNAs in animal models of MI, in human and animal plasma samples of MI (prognostic and diagnostic targets), and on miRNAs as promising therapeutic targets.

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INTRODUCTION

MicroRNAs (miRNAs) are endogenously expressed small non-coding RNA molecules. Genes encoding miRNAs can be found in genomes of almost all organisms, including viruses. Their prime mechanism of action is post-transcriptional repression of gene expression^[1]. It is suggested that the short length (22 nt) maximizes target-gene specificity and minimizes non-specific effects. It is estimated that miRNAs regulate approximately 30% of genes within the human genome^[2]. There are over 2000 miRNAs known to be encoded by human genome. All sequenced and cloned miRNAs from humans as well as from other species are included in database miRBase (v20.0, June 2013, <http://www.mirbase.org>). All known miRNAs from different species, including human, are collected in the miRBase^[3].

Mechanism of action of miRNAs

Biogenesis (including genes encoding miRNAs), transcription and processing are beyond the scope of this review and are described elsewhere^[1,2,4,5]. As mentioned above, miRNAs prime mechanism of action is repression of gene expression. By sequence-specific binding to the 3'-untranslated region (3'-UTR) of mRNAs, miRNA affects stability of the transcripts and cause mRNA degradation, which is the main mechanism in plants and happens when complementarity between miRNA and mRNA is perfect, or cause protein synthesis repression (translational repression), which happens when base pairing between these two molecules is incomplete and is the canonical mechanism in animals^[1,2,4,5]. Due to incomplete base pairing in animals and humans, each miRNA could influence translation of many different mRNAs without degrading it (*i.e.*, over 200 predicted target genes) and vice versa each mRNA may be influenced by different miRNA. It appears that the most efficient translational inhibition is provided through the multiplicity, which is the consequence of numerous target sites for the same miRNAs within 3'-UTR of the same mRNA (cooperative action of multiple identical miRNAs), and through cooperativity, which is due to numerous target sites for the different miRNAs within 3'-UTR of the same mRNA. miRNA access to the UTRs could be on one hand restricted by proteins or mRNA secondary structures, and on the other hand these structures and protein binding may facilitate recognition of the mRNA targets^[6]. Some miRNAs might also have other functions, although translational repression has been suggested to be the canonical one^[2,4].

miRNA in regulating physiological functions

Different approaches in *in vitro* and *in vivo* experiments have been used to reveal function of majority of miRNA. Using mutated miRNA or its mutated complementary site within mRNA, consequently disrupting regulation of mRNA by miRNA leads to the determination of the phenotypic consequence of this non-binding. An-

other possibility is use of transgenic constructs of either 3'-UTR or miRNA expressing vector and ectopic expression of the either miRNA or mRNA^[1,7]. Perhaps the best evidence that miRNA are playing a significant role in normal physiological functions was established, when the components of the miRNA biogenesis pathway were depleted^[8]. In normal cell conditions, miRNAs can repress translation in different ways: (1) as a switching-off for the targets, when protein production is reduced to inconsequential levels in a cell type, where target mRNAs should not be expressed; (2) as fine-tuning expression of target gene, when protein output can be adjusted in a way, which provides customized expression in one cell type and uniformly expressed level within another cell type; and (3) as neutralizers of and bystanders in target gene expression, when mRNA downregulation by miRNAs is negated through feedback processes^[1]. The role of miRNAs can be combinatorial (defined as cooperativity), different in different cell types, and either specific or housekeeping^[9].

Through the studies of expression profiling of normal and disease tissues it has been shown that miRNAs are expressed in spatial as well as in temporal manner. *miR-208* is a good example of expression in tissue-specific manner. Its expression can be detected specifically in the hearts, as well can be *miR-122* found specifically in the liver. As an example of cell-type-specific miRNAs are *miR-223*, which is primarily expressed in granulocytes, and *miR-1* and *miR-133*, which are believed to be myocyte-specific^[10]. miRNAs are involved in a myriad of biological processes, including proliferation, apoptosis, metabolism, differentiation, epithelial-to-mesenchymal transition, regulation of insulin secretion, division of stem cells, embryonic development and patterning, fetal growth, immune system, including resistance to viral infection and vice versa viral production (in a case of HCV), *etc.*^[8]. miRNA activity is believed to have crucial role in regulatory role in maintaining tissue identity during embryogenesis as well as in adult life. Distinct miRNA expression profile, with completely different gene expression patterns might be observed in every cell type at each developmental stage^[9-11].

Target prediction and bioinformatics

As mentioned above, miRBase is major database of all known miRNAs, which can also predict possible miRNA targets^[3]. Predicting possible miRNA binding sites for specific mRNAs or potential targets for certain miRNA is usually the first step in target identification and for this purpose numerous computational methods have been developed. Main characteristics that are included in established programs are: evolutionarily conservation of the complementary 3'-UTR sequence, quality and stability of mRNA:miRNA pairing and involvement of "seed sequence". It is believed that for base pairing the most important is "seed sequence" of the miRNA (2-8 nt at the 5'-end) and its interaction with seven consecutive nucleotides in the target mRNA^[12]. However, all pre-

dicted targets have to be validated *in vitro* and *in vivo* since none of these programs can independently validate the targets^[7,13]. Due to the facts that 3'-UTR sites with perfect complementarity to the miRNA are necessary functional and that mRNA sites with imperfect complementarity can themselves be very good miRNA targets, are bioinformatic analysis more prone to false positives^[6]. Therefore, experimental demonstration that overexpression of the miRNA represses a luciferase reporter fused to the 3'-UTR of the predicted target and that this repression is not established by point mutations in the 3'-UTR target sequence is the gold standard for miRNA target identification^[13,14]. Finally, association of mRNA:miRNA pairs with disease pathogenesis should be confirmed by expression profiling in human diseases by co-expression analyses^[7,14]. Human MicroRNA Disease Database identifies all disease-related miRNAs with their tissue expression patterns^[15]. Further, Tarbase lists experimentally validated miRNA targets for all organisms^[12].

miRNAs AND DISEASE

Mutations, single-nucleotide polymorphisms and the epigenetics of miRNAs

There are several genetic and epigenetic abnormalities within miRNA genes that might contribute to a wide range of diseases. These abnormalities include small- and large-scale genomic alterations, as are rearrangements and chromosomal translocations, copy-number variation, nucleotide expansion, and single-nucleotide polymorphisms (SNPs) that beside protein-coding region also affect regions that code for non-coding RNAs. First, it has been shown that approximately 50% of the miRNA genes are encoded within fragile chromosomal sites or sites that are prone to cancer-associated rearrangements^[10]. Second, although some SNPs are silent and cause no obvious functional consequence, other might cause disruption of binding between miRNAs and their targets, which can potentially lead to gain or loss of the function of miRNA or its target gene and consequently contribute to the disease state^[16]. Variants identified in miRNA or their precursors (pri-miRNA or pre-miRNA) that beside targeting might also affect the processing and expression of miRNAs, are rarely observed. However, potential of variation in miRNA target sites is more huge^[6,16]. Third, the aberrant DNA methylation of gene promoters has been shown to result in the inactivation of different genes, including miRNAs, and in parallel, miRNAs can also regulate proteins involved in DNA methylation^[17].

Aberrant expression of miRNAs

Epigenetic mechanisms and genomic abnormalities frequently lead to abnormal miRNA expression profiles thus causing pathogenetic events in diseases. Numerous advances in miRNA research and numerous expressions profiling of diseased human tissue are suggesting that miRNAs are associated with various pathological conditions. miRNAs have been linked to wide range of diseases,

including cancer genetic and immunological disorders, neurodegenerative and cardiovascular disorders^[10].

THERAPEUTIC POTENTIAL OF miRNAs

miRNA expression patterns are dynamically regulated during various diseases and can also be used for pharmacological manipulation. Studies have demonstrated that the systemic use of antagomirs is well suited to block miRNA function in small animal models. For targeting a specific miRNA or disrupting binding between miRNA and its target mRNA the chemically modified oligonucleotides have been developed. miRNAs as small molecules of approximately 22 nt in length are more feasible delivered *in vivo*. Synthetic miRNAs can be therefore delivered systematically and may thus serve as therapeutic targets in the future^[18].

Replenishing small RNAs

Underexpressed miRNA might be restored by reintroduction of the mature miRNA into the target tissue consequently restoring regulation of the miRNA target gene. miRNAs as potential therapeutic agents can be easily targeted and delivered to the appropriate tissue. Three major approaches are described below. Artificial miRNA or miRNA "mimics" enhance the expression of beneficial miRNAs. Artificial miRNAs are transient transfections of double-stranded miRNAs and possess the ability to bind to the homologous target site in various mRNAs. Another option is the introduction of a viral vector or plasmid expressing a specific miRNA from a short hairpin (sh) duplex (pre-miRNA-like shRNA). A high level of shRNA might lead to effective target knockdown; however, it may also saturate the miRNA biogenesis pathway and lead to off-target effects with fatal consequences. Therefore, another possibility arises, namely miRNA scaffolds. In scaffolds of endogenous pri-miRNA or pre-mRNA, siRNA is inserted and introduced to the target tissue leading to the degradation of homologous mRNA. This approach is advantageous in terms of specificity and stability over conventional shRNA because both siRNA and shRNA may trigger a non-specific interferon response in addition to any off-target effects. As an example in cardiovascular disease, overexpression of *miR-133* was used in a study of cardiac hypertrophy. By adenovirus delivery of a miRNA expression cassette, expression of *miR-133* was restored, which results in protection of experimental animals from agonist-induced cardiac hypertrophy^[18].

Inhibiting small RNAs

ASOs are short single-stranded antisense oligonucleotides, which are called anti-miRNA oligonucleotides, AMOs or antagomirs when talking about inhibition of miRNA. Antagomirs have been shown to efficiently and specifically silence endogenous miRNAs in mice. Overexpressed miRNA can also be downregulated by reducing the loop region of the miRNA precursor (pre-miRNA). The loop regions of different pre-miRNAs are not con-

served and might therefore limit their application. Another approach is to use miRNA sponges, which are miRNA inhibitory transgenes containing multiple tandem binding sites for an endogenous miRNA and can inhibit several closely related miRNAs. miRNA sponges may be useful for sequestering a miRNA family with overlapping and redundant targets. miR-masks and miR-erasers have also been developed. Similarly to a miR-sponge, a miR-eraser sequesters more than one miRNA, except that there are only two copies of the antisense sequence. For masking the miRNA binding site on the target gene, miR-mask or miRNA masking antisense approach has been designed, which forms a duplex with target mRNA. They are also called antisense oligodeoxynucleotides (ODNs). Two approaches have been used in the context of studying cardiovascular diseases. A miRNA decoy using miRNA sponges was designed and used in research studying the effect of *miR-133* in the pathogenesis of cardiac hypertrophy. Another approach used ODNs entirely complementary to the miRNA target motifs in the 3'-UTR of 2 cardiac pacemaker channel genes, *HCN2* and *HCN4*^[18,19].

Delivering miRNAs or its inhibitor to the target tissue

Current limitations exist in the following areas and need improvement: the efficiency of delivery to target tissues; systemic administration of drug; the potential inhibition of non-target genes (off-target effects); redundancy in the efficacy of different miRNAs; potential toxicity; and immunogenic responses. Modifications have improved the stability of miRNAs or blocked their inhibition (*i.e.*, nuclease resistance and pharmacokinetic properties such as half-life in serum and cellular uptake). Stabilization and facilitation of intravenous delivery of antagomirs could be improved by chemical modifications and cholesterol conjugations. However, toxicity due to chemical modifications should be taken into account. Local administration in easily accessible tissues has been used in the majority of the developed protocols; a major challenge remains for tissue- and cell-type-specific targeting. Viral and non-viral delivery systems have been developed in conjugation with homing signals for tissue- or cell-type-specific delivery, *e.g.*, linked to lipids and/or proteins, cationic liposomes, cholesterol, bacterial phage, aptamers, *etc*^[18,19].

miRNA IN MYOCARDIAL INFARCTION

MicroRNA in cardiovascular diseases

miRNAs contribute to the regulation of developmental, as well as physiological and pathological processes in the heart. Loss of cardiomyocyte renewal is a hallmark of numerous cardiac diseases, which might also influence miRNA expression patterns in the diseased heart^[20]. Primary studies of miRNA involvement in hypertrophy, heart failure and myocardial infarction analyzed miRNAs that are enriched in or are specific for cardiomyocytes; however, growing evidence suggest that other miRNAs, not cardiac- or muscle-specific, play a significant role in

cardiovascular disease^[21-24]. Using experimental animals and human samples dysregulation of specific miRNAs has been shown that are distinct than those involved in other heart diseases as are hypertrophy and heart failure (HF). Cell lines and animal models of different forms of myocardial ischemia, including myocardial infarction (MI), have been used to perform miRNA microarray expression profiling^[20]. It has been shown that in response to limited amount of oxygen, numerous miRNAs are up- or downregulated. Many of dysregulated miRNAs are dependent on a transcription factor that plays an important role in response to low oxygen, hypoxia-inducible-factor. Further analyses showed that oxidative stress also activates other transcription factors that beside miRNA expression influence different homeostatic and physiological processes as are metabolism, angiogenesis, cell survival and oxygen delivery^[25,26]. Numerous other pathways are activated in response to MI, including apoptosis and fibrosis, as well as numerous cell types such as cardiomyocytes, immune cells, fibroblasts and endothelial cells (ECs)^[27]. However, the majority of studies were performed in terms of expression analysis and target gene identification, with only one publication focusing on MI, specifically target site polymorphisms and the risk for MI.

Cardiac and muscle specific miRNAs in heart

There are five miRNAs recognized as muscle- and/or cardiac-specific or enriched, *miR-1*, *miR-133*, *miR-206*, *miR-208* and *miR-499*. For *miR-1* and *miR-133* it is believed that are expressed in muscle-specific pattern and that regulate heart development^[28]. *miR-208* has been identified as cardiac-specific and *miR-499* as cardiac-enriched.

In the current review we have focused on miRNAs involved in MI pathogenesis and their diagnostic, prognostic and therapeutic potential regarding MI. The function of various miRNAs analyzed in cell lines, animal models of MI and patients with MI are presented. Table 1 summarizes all miRNAs in experimental model of MI and human MI, describes their suggested function and predicted targets. We further overviewed the results of free-circulating miRNAs in different bodily fluids of patients and/or an animal model with MI. Table 2 summarizes all miRNAs as potential diagnostic and/or prognostic targets in MI. Lastly, therapeutic opportunities using miRNA strategies in the context of MI are also presented. More detailed description of all these miRNAs is below.

Cell line models

miR-21: *miR-21* was upregulated after inducing injury to cardiac myocytes using H₂O₂, and H₂O₂-induced cardiac cell death and apoptosis were increased by a *miR-21* inhibitor. Programmed cell death 4 (PDCD4) has been identified as a target of *miR-21*, and activator protein 1 (AP-1) has been identified as a downstream signaling molecule of PDCD4^[29]. All miRNAs with suggested role in apoptosis in MI are summarized in Figure 1.

Table 1 miRNAs with suggested role in experimental models of myocardial infarction and in myocardial infarction in humans

miRNA	Role/function	Expression in MI	Target genes	Species	Ref.
<i>miR-1</i>	After heat-shock protective against I/R	Nd	Repressing pro-apoptotic and up-regulating anti-apoptotic genes	Mouse	[40]
	Nd	Down	Nd	Mouse	[59]
	Pro-apoptotic	Up	Igf1	Rat	[45]
	Pro-arrhythmogenic	Up	Ion channels: Cx43, Kir2.1	Rat	[46]
	Predictive	Down, up	Predictive	Human	[55,56]
<i>miR-15b</i>	Anti-angiogenic	Down	Suggested VEGF and Ang2	Endothelial cells	[30]
<i>miR-21</i>	H ₂ O ₂ induced cell injury	Up	Pdcd4	Cardiomyocytes	[29]
	After heat-shock up, protective against I/R	Nd	Repressing pro-apoptotic and up-regulating anti-apoptotic genes	Mouse	[40]
	Response to I/R	Up in cardiac fibroblasts	Pten	Mouse	[23]
	Anti-apoptotic	Down, up	Pdcd4	Rat	[47]
	Pro-arrhythmogenic	Up	Sprouty-1, collagen I, III	Rat	[48]
<i>miR-24</i>	Anti-fibrotic	Down	Furin	Mouse	[35]
	Anti-angiogenic, induce endothelial cell apoptosis	Down in cardiomyocytes and fibroblasts, up in endothelial cells	Gata2, pak4	Mouse	[36]
			Enos	Mouse	[37]
	After heat-shock up, protective against I/R	Nd	Repressing pro-apoptotic and up-regulating anti-apoptotic genes	Mouse	[40]
<i>miR-29</i> family	Anti-fibrotic	Down	Proteins involved in fibrosis (COL1A1-2, COL3A1, FBN1, ELN)	Mouse, human	[34]
<i>miR-29b</i>	Anti-fibrotic	Down	Proteins involved in fibrosis (COL1A1, COL3A1, α SMA)	Rat	[52]
<i>miR-34a</i>	Pro-apoptotic	Up	Aldh2	Rat	[49]
<i>miR-92a</i>	Anti-angiogenic	Up	Itga5	Mouse	[38]
<i>miR-101a/b</i>	Anti-fibrotic	Down	Cfos	Rat	[50]
<i>miR-106b</i>	Anti-apoptotic	Up	P21	Cardiomyocytes	[30]
<i>miR-133a</i>	Nd	Down	Nd	Mouse	[59]
	Predictive	Down	Predictive	Human	[55,56]
<i>miR-133b</i>	Predictive	Down	Predictive	Human	[55,56]
<i>miR-146a</i>	Predictive: inflammation and VR	Up	Predictive	Human	[57]
<i>miR-150</i>	Predictive: inflammation and VR	Down	Predictive	Human	[57]
<i>miR-155</i>	Predictive: inflammation and VR	Down	Predictive	Human	[57]
<i>miR-206</i>	Pro-apoptotic	Up	Igf1	Rat	[45]
<i>miR-208a</i>	Nd	Down	Nd	Mouse	[59]
	Predictive	Up	Predictive	Human	[55]
<i>miR-320</i>	Pro-apoptotic	Down	Hsp20	Mouse	[41]
<i>miR-494</i>	Activation of Akt pathway	Down	Pro- and anti-apoptotic proteins (PTEN, ROCK1, camkii; FGFR2, LIF)	Mouse	[42]
<i>miR-499</i>	Nd	Down	Nd	Mouse	[59]
<i>miR-711</i>	Involved in anti-fibrotic effect of pioglitazone	Down	Sp1	Rat	[51]
<i>miR-874</i>	Regulated by Foxo3a in necrosis	Up	Caspase 8	Mouse	[39]

I/R: Ischemia/reperfusion; MI: Myocardial infarction; Nd: Not determinate; VR: Ventricular rupture.

***miR-15b* and *miR-106b*:** After retrieving 119 MI-related miRNAs from publications, GO and pathway analyses for their predicted gene targets demonstrated that these dysregulated miRNAs were enriched in cardiovascular-related phenotypes. By highlighting miRNA-gene networks, overall relationships between miRNAs and gene targets were discovered, particularly in apoptosis and angiogenesis. Experimental data identified *miR-106b* as an anti-apoptotic modulator through inhibition of p21 expression and *miR-15b* as an anti-angiogenic miRNA with the possible targets vascular endothelial growth factor and Ang2 (angiopoietin 2)^[30]. All miRNAs with suggested role in angiogenesis in MI are summarized in Figure 2.

To investigate the possible release of miRNAs from activated platelets, the miRNA content of platelets was screened from control patients and patients with MI.

Nine miRNAs found to be differentially expressed in MI patients compared with healthy controls were screened, and 8 of these were decreased in MI patients. Of these, *miR-22*, *miR-185*, *miR-320b* and *miR-423-5p* increased after aggregation in the supernatant of platelets and were depleted in thrombi aspirated from MI patients. Platelets from patients with MI exhibit a loss of specific miRNAs, and activated platelets shed miRNAs that can regulate EC gene expression^[31].

Mouse models

Whole genome microarray analysis: Genome-wide mRNA and miRNA expression profiles were performed at three time points post-MI: 2 d, 2 wk and 2 mo. The majority of differentially expressed miRNAs were uniquely regulated at each of the time points analyzed.

Table 2 miRNAs as potential diagnostic and prognostic biomarkers in myocardial infarction

miRNAs as potential biomarker	Role of biomarker	Expression in body fluid	Species and body fluid	Ref.
<i>let-7b</i>	Potential diagnostic value	Up	Plasma; human	[72]
<i>let-7f</i>	Differentiating TTC and MI	Down	Plasma; human	[79]
<i>miR-1</i>	Detection of AMI and AP	Up	Exosome, serum; human and mouse	[59]
	Correlation with MI size	Up	Serum; rat and human	[60]
	Differentiating AMI and AP	Up	Serum; human	[61]
	Differentiating AMI and other cardiovascular diseases	Up	Plasma; rat and human	[67]
	Similar time course to cTnI and the same trend to cTnI concentration	Up	Plasma and tissue; human and mouse	[68,70]
	Differentiating AMI and non-AMI	Up	Plasma; human	[69]
	AMI biomarkers, not superior to cTnT	Up	Plasma; human	[71]
	Associated with various degree of cardiovascular damage (AMI, viral myocarditis, diastolic dysfunction, acute HF)	Up	Plasma; human	[76]
	No association with 30 d mortality post-MI and diagnosis of HF	Up	Plasma; human	[81]
	Biomarker for AMI, correlated with renal elimination	Up	Plasma, urine; human, pig	[85]
<i>miR-16</i>	Detected in urine	Up	Urine; rat	[86]
	Differentiating TTC and MI	Down	Plasma; human	[79]
<i>miR-21</i>	Higher risk of impaired LV contractility	Up	Plasma; human	[83]
	Associated with various degree of cardiovascular damage (AMI, viral myocarditis, diastolic dysfunction, acute HF)	Nd	Plasma; human	[76]
	Differentiating NSTEMI and CHF	Up	Plasma; human	[78]
	Time-dependent changes 2-90 d post-MI	Down, up	Plasma; human	[80]
<i>miR-26a</i>	Differentiating TTC and MI	Down	Plasma; human	[79]
<i>miR-27a</i>	High risk of impaired LV contractility	Up	Plasma; human	[83]
<i>miR-29a</i>	Time-dependent changes 2-90 d post MI	Up	Plasma; human	[80]
<i>miR-29b</i>	Associated with various degree of cardiovascular damage (AMI, viral myocarditis, diastolic dysfunction, acute HF)	Nd	Plasma; human	[76]
<i>miR-30a</i>	Potential diagnostic value	Up	Plasma; human	[72]
<i>miR-30c</i>	Correlation with MI size	Up	Whole blood; human	[64]
<i>miR-34a</i>	Prognostic: correlated with LV end diastolic dimension	Up	Exosomes, serum; human	[62]
<i>miR-101</i>	Higher risk of impaired LV contractility	Down	Plasma; human	[83]
<i>miR-126</i>	The same trend to cTnI expression	Down	Plasma; human	[70]
	Positive association to the risk for MI	Nd	Plasma; human	[84]
<i>miR-133a</i>	Detection of AMI, AP: biomarker for cardiomyocyte death	Up	Exosome, serum; human and mouse	[59]
	AMI biomarker, correlation to cTnI	Up	Plasma and whole blood; human	[66]
	Differentiating AMI and other cardiovascular diseases	Up	Plasma; rat and human	[67]
	Similar time-course to cTnI	Up	Plasma and tissue; human and mouse	[68]
	AMI biomarkers, not superior to cTnT	Up	Plasma; human	[71]
	Differentiating AMI and AP, positive correlation to severity of coronary stenosis	Up	Plasma; human	[75]
	Associated with various degree of cardiovascular damage (AMI, viral myocarditis, diastolic dysfunction, acute HF)	Up	Plasma; human	[76]
	Differentiating TCC and MI	Up	Plasma; human	[79]
	Biomarker for AMI, correlated with renal elimination	Up	Plasma, urine; human, pig	[85]
<i>miR-133b</i>	Similar time-course to cTnI	Up	Plasma and tissue; human and mouse	[68]
<i>miR-134</i>	Differentiating AMI and AP	Up	Serum; human	[61]
<i>miR-145</i>	Correlation with MI size	Up	Whole blood; human	[64]
<i>miR-146a</i>	Associated with various degree of cardiovascular damage (AMI, viral myocarditis, diastolic dysfunction, acute HF)	Nd	Plasma; human	[76]
<i>miR-150</i>	Associated with LV remodeling	Down	Plasma; human	[82]
	Higher risk of impaired LV contractility	Down	Plasma; human	[83]
<i>miR-155</i>	Prognostic for cardiac death within 1 yr after MI	Up	Serum; human	[63]
	Associated with various degree of cardiovascular damage (AMI, viral myocarditis, diastolic dysfunction, acute HF)	Nd	Plasma; human	[76]
<i>miR-181c*</i>	Novel mirna dysregulated during MI	Nd	Whole blood; human	[65]

<i>miR-186</i>	Differentiating AMI and AP	Up	Serum; human	[61]
<i>miR-192</i>	Prognostic for development of ischemic HF	Up	Exosomes, serum; human	[62]
<i>miR-194</i>	Prognostic: correlated with LV end diastolic dimension	Up	Exosomes, serum; human	[62]
<i>miR-195</i>	Potential diagnostic value	Up	Plasma; human	[72]
<i>miR-197</i>	Negative association to the risk for MI	Nd	Plasma; human	[84]
<i>miR-208</i>	Differentiating AMI and AP	Up in AP compared to AMI	Serum; human	[62]
<i>miR-208b</i>	Differentiating AMI and other cardiovascular diseases	Up	Plasma; rat and human	[67]
	Time-dependent changes 2-90 d post MI	Up	Plasma; human	[80]
	Detected in urine	Up	Urine; rat	[86]
	AMI biomarkers, correlation to cTnT but not superior to cTnT	Up	Plasma; human	[71,76]
	Differentiating STEMI and NSTEMI	Higher in STEMI	Plasma; human	[73]
<i>miR-223</i>	Associated with various degree of cardiovascular damage (AMI, viral myocarditis, diastolic dysfunction, acute HF)	Up	Plasma; human	[76]
	Higher risk for 30 d mortality post MI and HF	Up	Plasma; human	[81]
	Biomarker for AMI, correlated with troponin	Up	Plasma, urine; human, pig	[85]
	Differentiating AMI and AP	Up	Serum; human	[61]
	Associated with various degree of cardiovascular damage (AMI, viral myocarditis, diastolic dysfunction, acute HF)	Down	Plasma; human	[76]
<i>miR-328</i>	Negative association to the risk for MI	Nd	Plasma; human	[84]
	AMI biomarker, correlation to cTnI	Up	Plasma and whole blood; human	[66]
<i>miR-380*</i>	Prognostic for cardiac death within 1 yr after MI	Up	Serum; human	[63]
<i>miR-423-5p</i>	Before PCI compared to after	Up	Plasma; human	[77]
<i>miR-499</i>	Differentiating AMI and AP	Up in AP compared to AMI	Serum; human	[61]
	Differentiating AMI and other cardiovascular diseases	Up	Plasma; rat and human	[67]
	Similar time course to cTnI	Up	Plasma and tissue; human and mouse	[68]
	AMI biomarkers, correlation to cTnT but not superior to cTnT	Up	Plasma; human	[71,76]
	Differentiating STEMI and NSTEMI	Higher in STEMI	Plasma; human	[73]
	Differentiating MI, CHF and unstable AP	Up	Plasma; human	[74]
	Associated with various degree of cardiovascular damage (AMI, viral myocarditis, diastolic dysfunction, acute HF)	Up and also in acute HF	Plasma; human	[76]
	Differentiating NSTEMI and CHF	Up	Plasma; human	[78]
	Higher risk for 30 d mortality post MI and HF	Up	Plasma; human	[81]
	Biomarker for AMI, correlated with renal elimination	Up	Plasma, urine; human, pig	[85]
	Novel miRNA dysregulated during MI	Nd	Whole blood; human	[65]
<i>miR-1915</i>	Prognosis after MI	Up and down	Serum; human	[63]
11 miRNAs	Predicting AMI (96% specificity; 90% sensitivity; 93% accuracy)	Up and down	Whole blood; human	[64]
20 miRNAs				
A subset of miRNAs	Dysregulated during AMI course	Nd	Whole blood; human	[65]
34 miRNAs	AMI biomarkers	20 up, 14 down	Plasma and tissue; human and mouse	[68]
19 candidate miRNAs	Prediction for risk of MI	Nd	Plasma; human	[84]

AMI: Acute myocardial infarction; AP: Angina pectoris; cTnI: Cardiac troponin I; CHF: Chronic heart failure; cTnT: Cardiac troponin T; HF: Heart failure; LV: Left ventricle; MI: Myocardial infarction; Nd: Not determine; NSTEMI: Non-ST-elevation MI; PCI: Percutaneous coronary intervention; STEMI: ST-elevation MI; TTC: Takotsubo cardiomyopathy.

Bioinformatic analysis demonstrated that several genes and miRNAs in various pathways are regulated in a temporal or phenotype-specific manner^[32]. In another study, a mouse MI was induced and one week after MI, a set of 29 upregulated miRNAs was found in the left ventricle originating from the *Dlk1*-deiodinase type 3 gene (*Dio3*) genomic imprinted region, which has been identified as a hallmark of pluripotency and proliferation. This miRNA signature was associated with an increase in expression of the *Dio3* located in this region. *Dio3* is a fetally expressed enzyme associated with cell proliferation, which was shown to be upregulated in cardiomyocytes. These data

suggest that a regenerative process is initiated, but not completed, in adult cardiomyocytes after MI^[33].

***miR-29* and fibrosis:** One of the first studies regarding MI was comparing expression profiles of miRNA from mouse border zone of the infarcted region as well as from the remote myocardium 3 and 14 d after MI. The *miR-29* family was downregulated in the region of the heart adjacent to the infarct. It has been shown that downregulation of *miR-29b* with anti-miRs induces the expression of collagen and that overexpression of *miR-29* reduces collagen. Three days after the MI, in

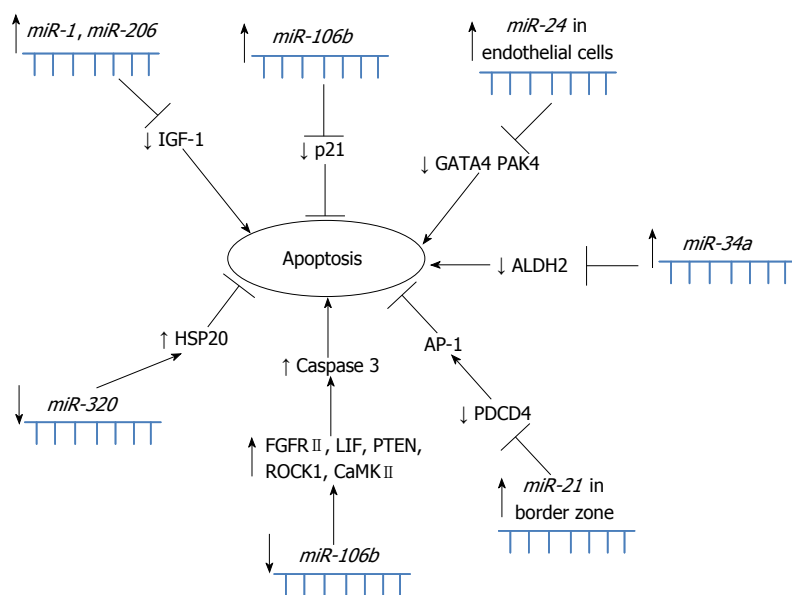


Figure 1 Schematic overview of miRNAs involved in apoptosis in myocardial infarction.

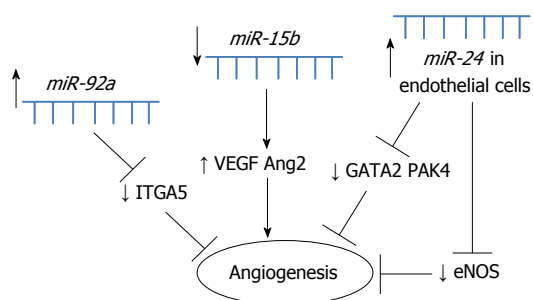


Figure 2 Schematic overview of miRNAs involved in angiogenesis in myocardial infarction.

the infarcted region, *miR-29* downregulation correlated with upregulation of collagen types I and III (COL1A1, COL1A2, COL3A1) and fibrillin, and in the remote myocardium expression of elastin was increased. The *miR-29* family was thus identified as a regulator of fibrosis^[34]. All miRNAs with suggested role in fibrosis in MI are summarized in Figure 3.

miR-24, fibrosis and angiogenesis: The downregulation of *miR-24* in a mouse MI model was closely related to extracellular matrix remodeling. Intra-myocardial injection of *miR-24* was able to improve heart function and attenuate fibrosis in the infarct border zone. *In vitro* experiments suggested that the upregulation of *miR-24* could reduce fibrosis and decrease the differentiation and migration of cardiac fibroblasts (CFs). Transforming growth factor β (TGF- β) increased *miR-24* expression, and overexpression of *miR-24* reduced TGF- β secretion and Smad2/3 phosphorylation in CFs. Furin was found to be a potential target for *miR-24* in fibrosis and both protein and mRNA levels of furin were regulated by *miR-24* in CFs^[35]. *miR-24* is markedly upregulated after cardiac ischemia and it has been also shown to be

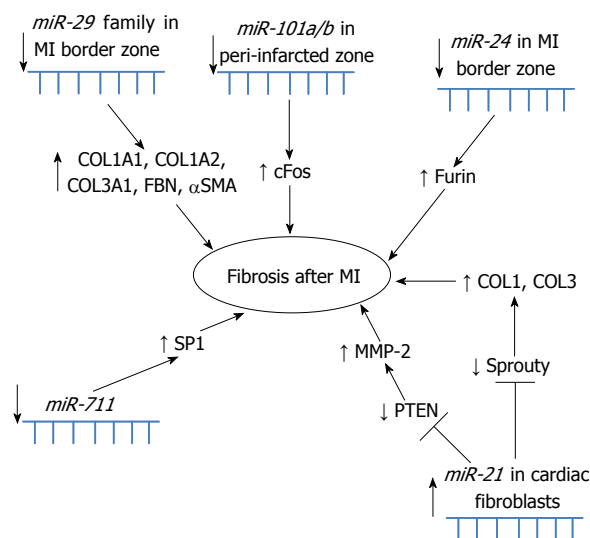


Figure 3 Schematic overview of miRNAs involved in fibrosis in myocardial infarction.

enriched in cardiac ECs. *miR-24* has been reported to induce apoptosis in ECs and abolishes endothelial capillary network formation by targeting the endothelium-enriched transcription factor GATA2 and the p21-activated kinase PAK4. MI size in mice has been limited by blocking endothelial *miR-24*. Reduced MI size as well as preserved cardiac function and survival were probably due to prevention of endothelial apoptosis and enhancement of vascularity as a consequence of blocked *miR-24*^[36]. Another mouse model showed that after a MI induction, *miR-24* expression was lower in the peri-infarct tissue and its resident cardiomyocytes and fibroblasts, while it increased in ECs. Local adenovirus-mediated *miR-24* decoy delivery increased angiogenesis and blood perfusion in the peri-infarct myocardium, reduced infarct size, induced fibroblast apoptosis and overall improved

cardiac function. The *miR-24* decoy increased apoptosis in cardiomyocytes. *In vitro* *miR-24* inhibition enhanced EC survival and proliferation and induced cardiomyocyte and fibroblast apoptosis. Endothelial nitric oxide synthase has been identified as a novel direct target of *miR-24* in human cultured ECs and *in vivo*^[37].

***miR-92a* and angiogenesis:** *miR-92a* has been shown to control the growth of new blood vessels (angiogenesis). Systemic administration of antagomir-92a led to enhanced blood vessel growth and functional recovery of damaged tissue. Overexpression of *miR-92a* blocked angiogenesis and vessel formation. *miR-92a* was shown to be upregulated after induction of acute MI (AMI). Antagomir-92a treatment reduced the infarct size, suppressed the number of apoptotic cells and augmented the number of *in vivo* perfused vessels in the infarct border zone. Among its targets are several pro-angiogenic proteins, including integrin subunit $\alpha 5$ ^[38].

***miR-874* and necrosis:** Another study revealed that in response to H₂O₂ treatment, *miR-874* was substantially increased. Knockdown of *miR-874* attenuated necrosis in the cellular model and also MI in the mouse model. The downstream mediator and target of *miR-874* was identified as caspase-8. Caspase-8 was able to antagonize necrosis. When suppressed by *miR-874*, caspase-8 lost the ability to repress the necrotic program. Foxo3a was identified as a transcriptional repressor of *miR-874* expression. This study determined a novel myocardial necrotic regulatory model consisting of Foxo3a, *miR-874* and caspase-8^[39].

***miR-1*, *miR-21*, *miR-24*, *miR-320* and ischemia-reperfusion:** Heat-shock treatment protects the heart against ischemia-reperfusion (I/R) injury. A significant induction and increase of *miR-1*, *miR-21* and *miR-24* has been observed in hearts of mice, which were subject to cytoprotective heat-shock (HS). miRNAs isolation from HS mice and injection into non-HS mice, resulted in significantly reduction of the infarct size in the heart following global I/R injury. Further analysis showed that reduction in MI size is accompanied by downregulation of expression of genes that induce apoptosis and upregulation of those that reduce apoptosis. These results showed that in the non-heat-shocked mice, miRNA function in heat-shock-like protection against I/R. Proposed mechanism of miRNAs action is through repression of pro-apoptotic genes (caspases 1, 2, 8, and 14, Bid, Bcl-10, Cidea, Ltbr, Trp53, and Fas) and induction of anti-apoptotic genes (Bag-3 and Prdx2). Through administration of *miR-21*, it has been shown that chemically synthesized miRNA can reduce MI size, an outcome that was blocked with a *miR-21* inhibitor^[40]. Another miRNA in the mouse hearts with I/R has been shown to be dysregulated, *miR-320*. *miR-320* was shown to be significantly decreased after MI and to target heat-shock protein 20. Experiments involving cardiac-specific overexpression of *miR-320* in trans-

genic mice resulted in increased apoptosis and infarct size in the hearts with I/R, and treatment with antagomir-320 reduced the infarct size^[41].

***miR-21*, I/R and fibrosis:** Further research on I/R models led to the identification of miRNAs with significant expression changes on days 2 and 7 post-I/R. Elevated *miR-21* levels were observed on day 2 as well as on day 7; however, *miR-21* induction in response to I/R was limited to CFs. CFs were shown to be the major cell type in the infarct zone. A marked decrease in phosphatase and tensin homolog (PTEN), a target of *miR-21*, has also been observed in the infarct zone. This decrease has been associated with increased matrix metalloproteinase-2 (MMP-2) expression, suggesting a *miR-21*-PTEN-Akt-MMP-2 pathway in CFs after MI^[23].

***miR-494* and apoptosis in I/R:** A mouse model with cardiac-specific *miR-494* overexpression showed improved recovery of contractile performance during the reperfusion period. This was accompanied by a reduction of apoptosis in transgenic mice and reduced MI in I/R. Cultured adult cardiomyocytes with short-term overexpression of *miR-494* showed an inhibition of caspase-3 activity and reduced cell death after stimulated I/R. *miR-494* inhibited three pro-apoptotic (PTEN, ROCK1, CaMK II) as well as two anti-apoptotic proteins (FGFR2 and LIF). *miR-494* targets both pro- and anti-apoptotic proteins and was downregulated in human infarcted hearts. Divergent targets of a miRNA may work unequally to balance a common signaling pathway and eventually affect its functional consequences^[42].

Rat models

Microarray analysis: Using genome-wide expression profiling of miRNAs in an ischemic myocardium from rat, seventeen miRNAs were shown to be significantly dysregulated during the AMI progression. Expression was analyzed 2, 7 and 14 d after AMI. On day 2, four miRNAs were upregulated (*miR-31*, *miR-223*, *miR-18a* and *miR-18b*) and two were downregulated (*miR-451* and *miR-499-5p*). On day 7, four miRNAs were upregulated (*miR-31*, *miR-214*, *miR-199a-5p* and *miR-199a-3p*) and seven were downregulated (*miR-181c*, *miR-181d*, *miR-499-5p*, *miR-29b*, *miR-26b*, *miR-126* and *miR-1*). On day 14, five miRNAs were upregulated (*miR-214*, *miR-923*, *miR-711*, *miR-199a-3p* and *miR-31*). Some of these dysregulated miRNAs were related to processes included in response to low oxygen as are hypoxia, inflammation, and fibrosis^[43]. In another study, propranolol was chronically administered to induce reversal of the MI. A long-term MI model in rats was established and microarray data analysis showed that long-term propranolol administration resulted in 18 of 31 dysregulated miRNAs undergoing reversed expression. *miR-1*, *miR-29b* and *miR-98* were suggested to play predominant roles in MI. Bioinformatic analysis suggested that *miR-1* regulates myocyte growth, *miR-29b* regulates fibrosis and *miR-98* regulates inflammation^[44].

miR-1 and miR-206 and apoptosis: The potential roles of muscle-specific *miR-1* and *miR-206* and their expression in a rat model of MI have been analyzed. Both miRNAs were significantly increased, while insulin-like growth factor 1 (IGF-1) protein levels were markedly reduced. Caspase-3 activity was increased in cells transfected with either *miR-1* or siRNA against IGF-1. Enhanced apoptosis could be therefore induced in cardiomyocytes with a low level of IGF-1 mediated by the post-transcriptional repression caused by *miR-1/miR-206*^[45].

miR-1 and arrhythmia: Propranolol was shown to reduce the incidence of arrhythmias in a rat model of MI. Increased expression of *miR-1* was observed in an ischemic myocardium. Administration of propranolol reversed the upregulation of *miR-1* to near control levels, significantly diminishing the incidence of arrhythmias in the first 12 h after MI. The suggested targets for *miR-1* were the cardiac ion channels Cx43 and Kir2.1^[46].

miR-21, apoptosis and atrial fibrillation: The miRNA expression profiling has been performed 6 h after AMI induction in rats. Thirty-eight miRNAs were dysregulated when infarcted area has been compared to non-infarcted heart tissue and 33 in the border zone of the MI when compared to non-infarcted area. *miR-21* was significantly downregulated in the infarcted area but was upregulated in the border zone (6 and 24 h after MI). *miR-21* had a protective effect on ischemia-induced cell apoptosis by targeting PDCD4 and AP-1, which might play critical roles in the early phase of AMI. Importantly, some miRNAs in the non-infarcted area were also differentially expressed 6 h after AMI, suggesting that in addition to dysregulated miRNAs in infarcted tissue and border zone, some miRNAs dysregulated in the remote myocardium might also contribute in the pathophysiological response to AMI^[47]. Another potential role of *miR-21* in the atrial fibrillation (AF) resulted from experimental HF after MI. *miR-21* was upregulated in atrial tissues following MI, along with the dysregulation of target genes sprouty-1, collagen-1, and collagen-3. Anti-*miR-21* treatment reduced atrial *miR-21* expression, decreased AF duration, and reduced atrial fibrous tissue^[48].

miR-34a and apoptosis: In an experimental rat model of MI, the expression of *miR-34a* was highly increased while the expression of aldehyde dehydrogenase 2 (ALDH2) was decreased. Overexpression of *miR-34a* in neonatal rat cardiomyocytes significantly enhanced apoptosis and downregulated ALDH2, suggesting that ALDH2 is a direct target of *miR-34a*. Serum *miR-34a* levels in AMI patients and rats were significantly higher than those in controls^[49].

miR-101, miR-711 and miR-29b, and fibrosis: Four weeks after MI induction in rats, examination of miRNAs expression in the peri-infarct area revealed downregulation of *miR-101a/b*. In rat neonatal CFs, enforced

expression of *miR-101a/b* lead to suppression of collagen production and proliferation. These effects were abrogated by co-transfection with antisense inhibitors of *miR-101a/b*. The fibroblast proto-oncogene c-Fos was suggested as a target of *miR-101a*. Anti-fibrotic action of *miR-101a* was mimicked by silencing c-Fos using siRNA, whereas effect of *miR-101a* in cultured CFs was cancelled by enforced expression of the c-Fos. In rats with chronic MI, four weeks after overexpression of *miR-101a* using adenovirus, remarkable improvement in cardiac performance was observed as well as reduction in interstitial fibrosis and inhibition of c-Fos and TGF- β 1 expression^[50]. Pioglitazone was further shown to increase *miR-711* expression and significantly reduce collagen- I levels similar to CFs, and overexpression of *miR-711* suppressed collagen- I levels. Therefore, pioglitazone may upregulate *miR-711* to reduce collagen- I levels in rats with MI. The *miR-711*-transcription factor SP1-collagen- I pathway may be involved in the anti-fibrotic effects of pioglitazone^[51]. Another fibrosis study has been performed showing that carvedilol protected against myocardial injury induced by AMI. In male rats, cardiac remodeling and impaired heart function were observed 4 wk after MI; the upregulation of Col1a1, Col3a1, and α -smooth muscle actin (SMA) mRNA was observed as well as the downregulation of *miR-29b*. Col1a1, Col3a1, and α -SMA were downregulated and *miR-29b* was upregulated by carvedilol in a dose-dependent manner in rat CFs. Enforced expression of *miR-29b* significantly suppressed Col1a1, Col3a1, and α -SMA expression^[52]. An alternative strategy has also been hypothesized that overexpression of *miR-29b*, which would inhibit mRNAs that encode CF proteins involved in fibrosis, would similarly facilitate progenitor cell migration into the infarcted rat myocardium. The number of GFP-positive cells, capillary density, and heart function were significantly increased in hearts overexpressing *miR-29b*, and downregulation of *miR-29b* with anti-*miR-29b* induced interstitial fibrosis and cardiac remodeling^[53].

Human MI

Microarray analysis: Our group performed genome-wide miRNA expression profiling of human MI (7 d post-MI and 4 wk post-MI) comparing fetal hearts to healthy adult hearts. A number of novel miRNAs were identified as well as some similar expression patterns between human MI and fetal hearts, suggesting involvement of cardiac gene reprogramming also in response after MI. Seven miRNAs were confirmed as dysregulated, including *miR-1*, *miR-133a/b*, *miR-150*, *miR-186*, *miR-210* and *miR-451*^[54].

miR-29: Several miRNAs were shown to be dysregulated in the murine MI model, including *miR-29*. Similarly dysregulation has been observed in human MI, after obtaining border zone of the infarcted cardiac tissue from the patients that received a cardiac transplant^[34].

miR-1, miR-133a/b, miR-208a: Our group further

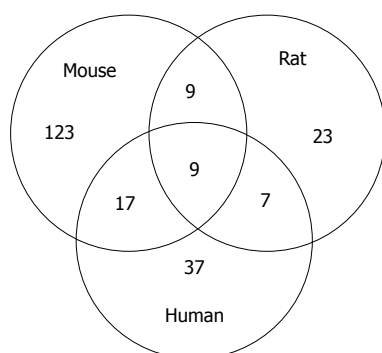


Figure 4 Venn's diagram of differentially expressed miRNAs in human myocardial infarction compared to mouse and rat model of myocardial infarction. Experimental data were obtained from microarray analysis performed on mouse model of MI^[32,33], rat model of MI^[43,44] and human MI^[54,58]. MI: Myocardial infarction.

showed that *miR-1*, *miR-133a/b* and *miR-208* were differentially expressed in human MI and fetal hearts when compared to healthy adults. Time-course changes were observed in human MI, with *miR-208* upregulated across all time points and *miR-1* and *miR-133a/b* downregulated 2-7 d after MI. All four miRNAs were downregulated in fetal hearts in comparison to healthy adults. We have also observed some similar patterns of miRNA expression between fetal hearts and MI^[55]. The remote myocardium was also analyzed and compared to healthy adult hearts and the infarcted area. Whereas *miR-1* expression was similar in MI and healthy adults, it was upregulated in the remote myocardium. Downregulation of both *miR-133a* and *miR-133b* was observed in the infarcted tissue as well as in the remote myocardium of patients with MI when compared to healthy adult hearts^[56].

miRNAs and ventricular rupture: Evidence suggests that an intense inflammatory reaction after a MI might contribute to the development of ventricular rupture (VR). In 50 patients with either healthy adult hearts or with MI (with or without VR), we showed an altered expression of *miR-146a*, *miR-150* and *miR-155*. *miR-146a* showed upregulation and *miR-150* and *miR-155* showed downregulation in patients with VR compared to those without. These miRNAs are involved in the regulation of innate immunity and the inflammatory response, providing further evidence that innate immunity resulting in an intense inflammatory reaction plays an important role in the pathogenesis of VR after a MI in humans^[57].

miRNAs and SERCA2: In another study our group also showed 43 dysregulated miRNAs and decreased expression of the protein SERCA2 when infarcted tissue was compared to the corresponding remote myocardium. The prediction of miRNA binding to SERCA2 identified 213 putative miRNAs. miRNA annotation of dysregulated miRNAs revealed 18 functional and 21 disease states that are linked to the cardiovascular diseases. Half of the dysregulated miRNAs were associated with SERCA2. Free-energy binding and flanking regions were defined for 10

upregulated miRNAs (*miR-122*, *miR-320a/b/c/d*, *miR-574-3p/-5p*, *miR-199a*, *miR-140* and *miR-483*). The dysregulation of 9 miRNAs was confirmed (*miR-21*, *miR-122*, *miR-126*, *miR-1*, *miR-133*, *miR-125a/b* and *miR-98*)^[58].

Comparison of the number of differentially expressed miRNAs from microarray studies performed on human MI^[54,58] and on mouse^[32,33] and rat model of MI^[43,44] is summarized in Figure 4. Only a small proportion of differentially expressed miRNAs overlaps between three different species, these are *let-7b*, *let-7f*, *miR-26b*, *miR-126-3p*, *miR-126-5p*, *miR-195*, *miR-199a-3p*, *miR-214* and *miR-451*. All these microarray analyses were performed at different time point post-MI. However, comparison has been performed including any dysregulated miRNA at any time point post-MI within species.

Circulating miRNAs

Serum and exosome miRNAs as AMI biomarkers:

In patients with AMI as well as in patients with angina pectoris (AP), significant increase in serum levels was observed for *miR-1* and *miR-133a*. *miR-133a* has been recognized as a circulating marker for cardiomyocyte death, because its elevated expression is observed in patients with an injured myocardium. Using an experimental mouse model, it was further identified that significant reduction in levels of *miR-1*, *miR-133a*, *miR-208a* and *miR-499* occur in the infarcted myocardium. After stimulation of cardiomyoblasts, exosome fraction of the culture medium was obtained. The measurement of *miR-133a* was performed. Significant elevation of *miR-133a* was observed upon the detection of cell death^[59]. Using an *in vitro* cardiac cell necrosis model, it was shown that cardiac *miR-1* was released into the culture media 20 min after induction, where it is stable for at least 24 h. The amount of *miR-1* released was related to the number of necrotic cardiac myocytes. Furthermore, a time-course study of serum *miR-1* in a rat model included time points at 1, 3, 6, 12, 24 h, and 3, 7, 14, 21 and 28 d after AMI. Serum *miR-1* levels were increased after AMI with a peak at 6 h, returning to the basal level 3 d after AMI, and showed a strong positive correlation with MI size. Research in humans has shown that in 31 patients with AMI, *miR-1* was significantly increased within 24 h after AMI and showed a positive correlation with serum creatine kinase-MB, suggesting its relationship to MI size also occurs in humans. At days 3 and 7, the serum levels returned to baseline^[60]. In another study, serum samples were taken from 117 patients with AMI, 182 patients with AP and 100 age- and gender-matched controls. The profiles of six serum miRNAs, *miR-1*, *miR-134*, *miR-186*, *miR-208*, *miR-223* and *miR-499*, were identified as AMI biomarkers and presented significant differences between the AMI and AP cases. *miR-208* and *miR-499* showed higher expression in the AP cases than in the AMI cases^[61].

Serum miRNAs and prognosis after MI: Using sera collected a median of 18 d after AMI onset, miRNAs were screened in 21 patients who experienced develop-

ment of HF within 1 year after AMI and in 65 matched controls. *miR-192*, *miR-194* and *miR-34a*, all p53-responsive miRNAs, were coordinately increased, particularly in exosomes. The serum level of *miR-192* was significantly upregulated in AMI patients with development of ischemic HF. *miR-194* and *miR-34a* expression levels were significantly correlated with the left ventricular (LV) end-diastolic dimension 1 year after AMI^[62]. The prognostic impact of circulating miRNAs in patients who survived AMI was also analyzed by a high-throughput array consisting of 667 miRNAs. Eleven miRNAs were differentially expressed in the serum from patients at high-risk for cardiac death, and a subset of circulating miRNAs might be predictive for cardiac death in post-AMI patients. Serum levels of *miR-155* and *miR-380** were higher in patients who experienced cardiac death within 1 year after discharge^[63].

Whole blood miRNAs as biomarkers of AMI: After performing miRNA expression profiling in peripheral whole-blood samples of patients with AMI, 121 dysregulated miRNAs have been identified. These miRNAs possess a unique signature of 20 miRNAs predicting AMI with 96% specificity, 90% sensitivity and 93% accuracy. *miR-30c* and *miR-145* levels were expressed in correlation with infarct size, which was estimated by release of Troponin T (TnT). Identification of miRNAs that is not based solely on the release of miRNAs from a necrotic myocardium is important for understanding active processes involved in the pathogenesis of MI (inflammation, plaque, rupture and vascular injury). Dysregulated miRNAs in AMI might be equally derived from other cellular populations that play an active role in AMI pathophysiology^[64]. To characterize temporal expression patterns of miRNAs in MI, another study was performed with miRNA expression levels measured at multiple time points (0, 2, 4, 12, 24 h after the initial presentation) in patients with acute MI. A subset of miRNAs was found to be significantly dysregulated both at the initial presentation and during the course of AMI. Novel miRNAs that are dysregulated early during MI were identified (*miR-1915* and *miR-181c**)^[65].

Whole blood and plasma miRNAs as biomarkers for MI: The whole blood and plasma samples were obtained from 51 AMI patients and compared with 28 control subjects. Sample collection from AMI patients was performed within 24 h and 7 d after the onset of AMI. In plasma as well as in whole blood from AMI patients, elevated *miR-133* and *miR-328* levels was observed. Seven days after onset of AMI symptoms increased circulating *miR-133* and *miR-328* levels returned to control levels. There has also been observed a correlation between cardiac Troponin I (cTnI) and circulating *miR-133* or *miR-328*^[66].

Plasma miRNAs as biomarkers for MI in humans: In AMI rats, plasma samples were taken at 1, 3, 6, 12

and 24 h. At these time points, measurement of levels of *miR-1*, *miR-133a*, *miR-499* and *miR-208a* has been performed. All these miRNAs were significantly increased, at least at one time point. *miR-208a* was undetectable at time 0 h, increased 1 h after AMI and reached its peak at 3 h. At time point 6-12 h, it began decreasing and at 24 h it was undetectable. At time point 1-3 h, *miR-1*, *miR-133a* and *miR-499* were elevated, at 3-12 h reached their peak and at 12-24 h finally decreased. *miR-1*, *miR-133a*, *miR-499* and *miR-208a* were present at very low levels or were absent in the plasma of healthy people, but were substantially higher in the plasma of 33 AMI patients compared with that of patients with other cardiovascular diseases, whereas *miR-208a* remained undetectable in patients with non-AMI heart diseases^[67]. In another study, miRNAs were analyzed in human plasma, mouse plasma and mouse cardiac muscle. A microarray analysis showed 20 upregulated and 14 downregulated miRNAs in 17 healthy donors compared with 33 patients with AMI. *miR-1*, *miR-133a/b* and *miR-499-5p* were upregulated and *miR-122* and *miR-375* were downregulated 6-12 h after MI onset. Five days later, all miRNAs were back to basal plasma levels, except that *miR-122* was lower than in controls through day 30. Compared to cTnI, peak expression was observed at a similar time in MI patients for *miR-1* and *miR-133a/b*, but *miR-499-5p* showed a slower time course. In mice, the pattern of upregulated miRNAs was similar to that in MI patients, but reciprocal expression was observed in cardiac tissue 3-6 h after MI^[68]. *miR-1* level was measured in a larger cohort of patients (159) with or without AMI. In the plasma from AMI patients, *miR-1* was significantly increased when compared with non-AMI patients. Its levels decreased to normal after medication. Statistical analysis revealed that elevated levels of circulating *miR-1* were not in correlation to patient characteristics (established biomarkers for AMI, concurrent disease as are blood pressure and diabetes mellitus or either age or gender)^[69]. Increased *miR-1* and decreased *miR-126* expression were consistently observed in the plasma from 17 patients with AMI compared with 25 healthy subjects. cTnI, *miR-1* and *miR-126* expression levels showed the same trend^[70]. *miR-1*, *miR-133a*, *miR-208b* and *miR-499* were further compared to cTnT for diagnostic value. Study has been performed on 67 patients with AMI and 32 healthy volunteers. Plasma samples from these subjects were collected. The levels of all plasma miRNAs were significantly higher in AMI patients than in healthy volunteers. At the time of hospital discharge of AMI patients, expression of the cardiac-specific miRNAs was reduced decreased to near baseline levels. However, it has turned out that for the diagnosis of AMI, the four plasma miRNAs were not superior to cTnT^[71]. In another study, plasma samples were obtained from 18 patients with AMI and 30 healthy adults. In this cohort of samples, *miR-30a*, *miR-195* and *let-7b* levels were examined. At time points 4 h, 8 h and 12 h after the onset of AMI, circulating *miR-30a* was highly elevated. In AMI patients, *miR-195* was also highly expressed, when

compared to control, but only at time points 8 h and 12 h. Through all the time points, *let-7b* was lower in AMI patients when compared to control samples. All three investigated circulating miRNAs, *miR-30a*, *miR-195* and *let-7b*, showed the peak expression at 8 h and were of significant diagnostic value for AMI^[72].

Plasma miRNAs for differentiating MI in humans:

Plasma concentrations of cardiac-enriched *miR-208b* and *miR-499* were measured in a case-control study of 510 MI patients and 87 healthy controls. *miR-208b* and *miR-499* showed elevated expression in patients with MI and nearly undetectable in healthy controls. In 397 patients with ST-elevation MI (STEMI), miRNAs had higher concentrations than in 113 patients with non-STEMI (NSTEMI)^[73].

Plasma miRNAs for differentiating MI from other cardiovascular diseases:

In all individuals with AMI, the concentration of plasma *miR-499* was shown to be increased; however it was below the detection limit in other groups of patient [control, chronic HF (CHF), and unstable AP]^[74]. The expression level of plasma *miR-133a* has been analyzed in 13 AMI patients, 176 AP patients and 127 control subjects for its relationship to the severity of coronary stenosis. The results showed that circulating *miR-133a* levels were significantly increased in AMI patients in a time-dependent manner, achieving a peak at 21.6 ± 4.5 h after the onset of AMI symptoms and showed a similar trend as the level of plasma cTnI. Importantly, the levels of circulating *miR-133a* positively correlated with the severity of coronary artery stenosis^[75]. Another study showed that plasma levels of *miR-1*, *miR-133a*, *miR-208b* and *miR-499* (muscle- or cardiac-specific or enriched miRNAs), *miR-21* and *miR-29b* (fibrosis-related miRNAs) *miR-146*, *miR-155*, *miR-223* (leukocyte-associated miRNAs) are associated with different degrees of cardiac injury as are AMI, acute HF, diastolic dysfunction and even viral myocarditis. In the plasma of 32 patients with AMI, *miR-208b* and *miR-499* were highly elevated compared with control subjects and both correlated with plasma cTnT levels. Both miRNAs also showed significant but milder elevation in viral myocarditis. However, in patients with acute HF, only *miR-499* showed significant elevation, whereas no significant change was observed in diastolic dysfunction^[76]. Another study group consisted of 17 patients with AMI, 4 with stable coronary artery disease (CAD) and 5 with no history of CAD. Expression of *miR-423-5p*, *miR-208* and *miR-1* was measured in plasma before percutaneous coronary intervention (PCI), at 6, 12 and 24 h. In stable CAD, the expression of *miR-1*, *miR-208a* and *miR-423-5p* did not show any significant differences at any time point. There was a higher number of *miR-423-5p* copies in patients with AMI before the PCI. However, 6, 12 and 24 h after PCI, the expression levels were similar to the control group and significantly lower than the baseline level. The expression levels of *miR-1* and *miR-208a* were not significantly different from the control

group^[77]. In another study, the increased expression levels of *miR-1*, *miR-21*, *miR-133a*, *miR-423-5p* and *miR-499-5p* has been showed in plasma of 92 patients with NSTEMI compared to 99 age-matched healthy control subjects. *miR-499-5p* and *miR-21* showed increased expression in NSTEMI compared to 81 patients with CHF. *miR-499-5p* also showed good diagnostic accuracy in differentiating patients with NSTEMI and CHF^[78]. Takotsubo cardiomyopathy (TTC) is clinically indistinguishable from AMI, and no established biomarkers are available for the early diagnosis of TTC and differentiation from AMI. After miRNA profiling, eight miRNAs were selected for verification in 36 patients with TTC, 27 patients with AMI and 28 healthy controls. Upregulation of *miR-16* and *miR-26a* was confirmed in patients with TTC compared with healthy subjects, and upregulation of *miR-16*, *miR-26a* and *let-7f* was observed in TTC compared with MI patients. Compared with healthy controls, *miR-1* and *miR-133a* showed upregulation in patients with MI, and *miR-133a* was substantially increased in patients with MI when compared with TTC. A unique signature comprising *miR-1*, *miR-16*, *miR-26a* and *miR-133a* differentiated TTC from healthy subjects and from MI patients^[79].

Plasma miRNAs and prognosis after MI: Plasma *miR-1*, *miR-21*, *miR-29a*, *miR-133a* and *miR-208* were measured in 12 age-matched reference controls and 12 post-MI patients from day 2 through day 90 post-MI. After MI, a progressive increase of LV end-diastolic volume was accompanied by time-dependent changes in specific miRNAs. Two days post-MI, *miR-21* decreased and 5 d post-MI increased. At later time points its expression level reached the control values. Similarly, at day 5 post-MI, *miR-29a* increased and then decreased to the control level at later time points. *miR-208* showed elevated expression at day 5 post-MI and did not show any decrease up to day 90 post-MI^[80]. *miR-1*, *miR-208b* and *miR-499-5p* were further measured in plasma samples from 424 patients for discrimination of a clinical diagnosis of MI and for association with 30-d mortality and for diagnosis of HF. Discrimination of MI was accurate for *miR-208b* and *miR-499-5p* but was considerably lower than for TnT. Increased miRNA levels were strongly associated with an increased risk of mortality or heart failure within 30 d for *miR-208b* and *miR-499-5p*, but the association was lost when adjusting for TnT^[81]. In another study, circulating miRNAs were measured in 90 patients after AMI and several miRNAs were identified as potentially involved in LV remodeling. *miR-150* was downregulated in patients with remodeling compared with patients without. *miR-150* outperformed B-type natriuretic peptide (BNP) to predict remodeling and reclassified 54% of patients misclassified by BNP and 59% of patients misclassified by a multi-parameter clinical model^[82]. Furthermore, plasma samples from 150 patients with AMI were obtained for determination of the levels of *miR-16*, *miR-27a*, *miR-101* and *miR-150*. A combination of the four miRNAs improved the prediction of LV contractility based

on clinical variables. Patients with low levels of *miR-150* or *miR-101* and elevated levels of *miR-16* were at high risk for impaired LV contractility. The four-miRNA panel reclassified a significant proportion of patients, with a net reclassification improvement of 66%^[83].

Plasma miRNAs and prospective study for MI: The association between baseline levels of miRNAs, the incidence of MI, and the cellular origin of miRNAs was analyzed in 820 participants with 19 candidate miRNAs. Three miRNAs were consistently and significantly related to the incidence of MI; *miR-126* showed a positive association, *miR-223* and *miR-197* were negatively related to the risk of disease. Control group consisted of healthy volunteers, in who limb I/R was performed by thigh cuff inflation. After obtaining plasma samples at baseline, 10 min, 1 h, 5 h, 2 d, and 7 d, miRNA expression was analyzed. Six distinct miRNA clusters were identified by computational analysis, and one of them consisted of all miRNAs that were related to the risk of a future MI. This cluster included miRNAs predominantly expressed in platelets and its characteristic was activation 1 h post-I/R (early) and activation 7 d post-I/R (sustained). Platelets were suggested as being a major contributor to this miRNA expression pattern, since in subjects with a subsequent MI, dysregulated patterns of circulating miRNAs occurred with endothelium-enriched *miR-126*^[84].

Plasma and urine miRNAs: In a pig I/R model, *miR-1*, *miR-133a* and *miR-208b* increased rapidly in plasma with a peak at 120 min, while *miR-499-5p* remained elevated longer. In humans, 25 patients with MI revealed that all four miRNAs were increased in plasma, with a peak by 12 h. Peak values of *miR-208b* correlated with peak troponin levels. *miR-1* and *miR-133a* both correlated strongly with renal elimination, which was confirmed by detection of *miR-1* and *miR-133a*, but not *miR-208b* or *miR-499-5p*, in the urine^[85].

Urine miRNAs: Blood protein MI biomarkers [creatinine phosphokinase-muscle band, TnT and TnI] are not typically filtered into urine. Urine *miR-1* was quickly increased in rats with a peak at 24 h after AMI and returned to the basal level 7 d after AMI. No *miR-208* was observed in normal urine; however, *miR-208* was easily detected in urine from rats with AMI. Serum exosomes from rats after AMI were isolated and injected into the circulating blood of normal rats; urine *miR-1* was significantly increased in the exosome-injected animals. The levels of urine *miR-1* were also significantly increased in patients with AMI^[86].

In summary, it has been shown that miRNAs may be useful circulating biomarkers for the diagnosis of AMI, differentiating them from other cardiovascular diseases and prognoses after MI. However, two studies have shown that miRNAs are not useful circulating biomarkers for some aspects of MI, and for prognosis of patients with STEMI or an incidence of LV remodeling 1 year

after anterior AMI^[87,88].

Therapeutic opportunities

All miRNAs as potential therapeutic targets were tested in mouse or rat models of MI. miRNAs and different therapeutic approaches analyzed in mouse model of MI are summarized in Figure 5 and miRNAs and different therapeutic approaches analyzed in rat model of MI are overviewed Figure 6.

***miR-181a* and skeletal myoblast transplantation in rats with MI:** A lentiviral siRNA against the loop region of *miR-181a* was shown to upregulate the skeletal myoblast (SKM) differentiation repressor Hox-A11 and reduce arrhythmias following SKM transplantation into ischemic myocardia of rats. Engraftments of SKMs with *miR-181a* knockdown improved cardiac function and significantly decreased the arrhythmogenic effect of SKM transplantation in rats with experimental MI^[89].

***miR-210* and treatment of ischemic heart disease:** *miR-210* was highly expressed in mouse cardiomyocytes that survived 48 h after hypoxia exposure compared with apoptotic cardiomyocytes. Mice receiving a *miR-210* precursor showed significant improvement of LV fractional shortening after 8 wk. Histological analysis showed decreased cellular apoptosis and increased neovascularization. Two target genes involved in inhibition of angiogenesis/vascular remodeling and induction of apoptosis, Ephrin-A3 and Ptp1 (non-receptor phospho-tyrosine protein phosphatase), were confirmed. It has been shown that *miR-210* can improve angiogenesis, inhibit apoptosis and improve cardiac function in a mouse model of MI^[90].

Phosphoinositide-3-kinase-regulated miRNA and mRNA: Activation of phosphoinositide-3-kinase (PIK3) is considered a new strategy for the treatment of heart failure and MI. To identify cardiac-selective miRNAs and mRNAs that mediate the protective properties of PIK3, experimental mice were used and identified growth factor receptor-bound protein (Grb14) gene expression that positively correlated with cardiac function. Grb14 is highly expressed in the mouse heart compared with other tissues. Three miRNAs were also highly correlated with Grb14, namely *miR-210*, *miR-34a* and *miR-222*^[91].

Tanshinone and miR-1: Accumulating evidence suggests that tanshinone II A can reduce the ischemic area and improve cardiac function and has been shown to suppress *miR-1* expression. Using a rat model of MI, tanshinone II A was administered daily for 7 d before MI and lasted for 3 mo following MI. Tanshinone II A was shown to relieve ischemia-induced injury, decrease the elevated *miR-1* levels in ischemic and hypoxic cardiomyocytes, and consequently restored the normal level of the *miR-1* target Cx43. In ischemic and hypoxic cardiomyocytes, tanshinone II A also inhibited activated p38 MAPK, SRF and MEF2^[92].

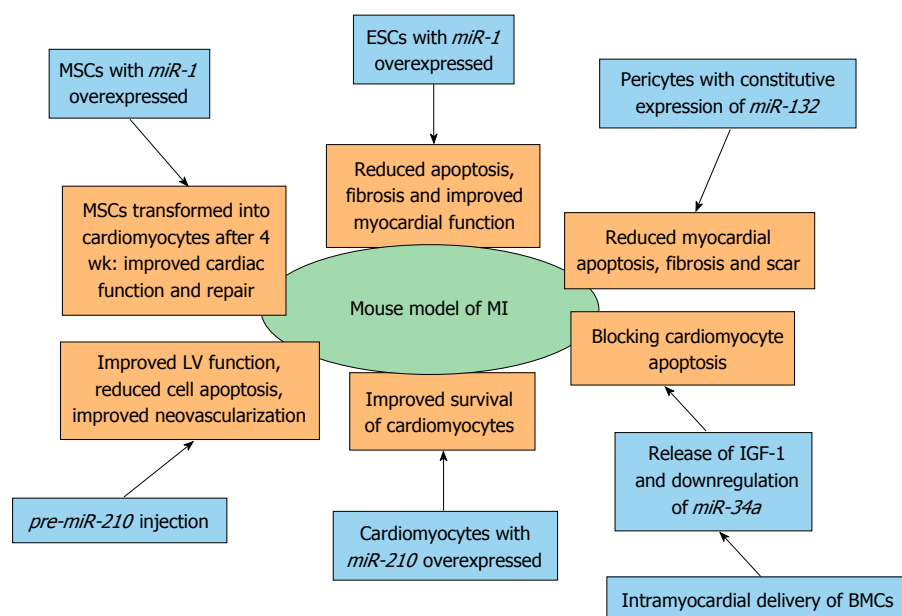


Figure 5 Therapeutic opportunities of miRNAs in myocardial infarction identified by using mouse model of myocardial infarction. BMC: Bone marrow cell; ESC: Embryonic stem cell; LV: Left ventricle; MSC: Mesenchymal stem cell; MI: Myocardial infarction; IGF-1: Insulin-like growth factor 1.

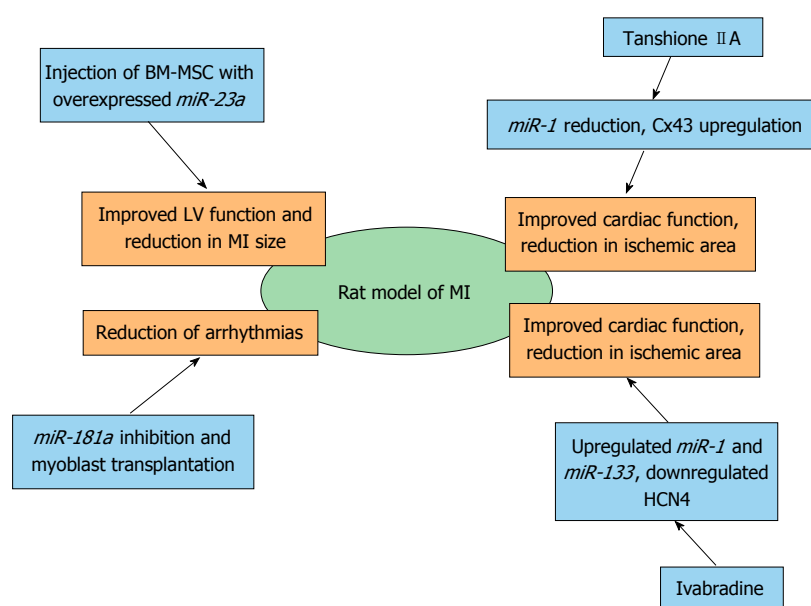


Figure 6 Therapeutic opportunities of miRNAs in myocardial infarction identified by using rat model of myocardial infarction. BM-MSC: Bone marrow-mesenchymal stem cell; LV: Left ventricle; MI: Myocardial infarction.

Ivabradine and *miR-1* and *miR-133a*: Ivabradine is a selective inhibitor of the hyperpolarization-activated, cyclic nucleotide-gated pacemaker current. Its effect on electrophysiological remodeling of myocytes from post-MI rats was observed as a decrease in the transcription of HCN4, a target of *miR-1* and *miR-133a*. Both, *miR-1* and *miR-133* were significantly elevated in myocytes. The beneficial effects of ivabradine may be due to the reversal of electrophysiological cardiac remodeling by reducing the overexpressed HCN channels in post-MI rats^[93].

Embryonic stem cells and miRNAs: Embryonic stem

cells (ESC) with overexpressed *miR-1* were transplanted into the infarcted myocardia of experimental animals, and reduced apoptosis was subsequently observed 4 wk post-MI. A significant elevation in p-Akt levels and diminished PTEN levels were also observed. The mice also had a significant improvement in some physiological cardiac functions^[94]. The same author investigated whether overexpression of *miR-1* in ESCs would enhance cardiac myocyte differentiation following transplantation into the infarcted myocardium. Two weeks after transplantation into the border zone of the infarcted heart, cardiac myocyte differentiation, adverse ventricular remodeling,

and cardiac function were assessed. Overexpression of *miR-1* in transplanted ESCs protected the host myocardium from MI-induced apoptosis. A significant reduction in interstitial and vascular fibrosis was observed as well as significantly improved heart function^[95].

Mesenchymal-stem cells and miRNAs: One week after MI, mice were intramyocardially injected at the heart infarcted zone with *miR-1*-transduced mesenchymal-stem cells (MSCs). At 4 wk post-transplantation, transplanted MSCs were able to differentiate into cardiomyocytes in the infarcted zone. Cardiac function with the *miR-1*-transduced MSCs was significantly improved, and treatment of MSCs expressing *miR-1* was more effective for cardiac repair, most likely by enhancing cell survival and cardiac myocyte differentiation compared with the MSCs without *miR-1*^[96]. *In vitro* co-culture between cardiomyocytes and MSCs has been established to test whether MSCs deliver *miR-210* to host cardiomyocytes; this showed co-localization of *miR-210* with the gap-junction protein Cx43. *miR-210* has been proposed to be transferred through gap junctions. Higher survival rates of cardiomyocytes co-cultured with MSCs was observed with concomitant expression of caspase-8 associated protein 2 (CASP8AP2) suggesting that *miR-210* translocates from MSCs to protect host cardiomyocytes. Direct transfer of pro-survival *miR-210* from MSCs to host cardiomyocytes led to a functional recovery of the ischemic hearts of the experimental animals^[97]. The clinical application of MSC-based therapy is restricted because of the poor survival of implanted cells. Using a tumor necrosis factor α -(TNF- α)-induced bone marrow (BM)-MSC injury model and a rat MI, it has been shown that *miR-23a* was involved in TNF- α -induced BM-MSC apoptosis through regulating caspase-7 and that the injection of BM-MSCs overexpressing *miR-23a* could improve LV function and reduce the infarct size in the rat MI model^[98].

Bone marrow cells and *miR-34a*: Cell therapy with bone marrow cells (BMC) can improve the recovery of cardiac function after ischemia and intra-myocardial delivery of BMCs in infarcted mice has been shown to regulate the expression of miRNAs in the heart and downregulate the expression of *miR-34a*, a pro-apoptotic miRNA. Transplanted BMCs regulate cardiac miRNAs by paracrine mode and thus contribute to the protective effects. IGF-1 inhibits the *miR-34a* processing and is released by BMCs, thereby blocking apoptosis in cardiomyocytes^[99].

Pericytes and *miR-132*: Pericytes are key regulators of vascular maturation and therapeutic activity, and mechanistic targets of saphenous vein-derived pericyte progenitor cells (SVPs) have been investigated using a mouse MI model. Transplantation of SVPs into the peri-infarct zone of mice attenuated LV dilatation, reduced myocardial scar, cardiomyocyte apoptosis and interstitial fibrosis, and blood flow and neovascularization. *miR-132*

was constitutively expressed and secreted by SVPs and markedly upregulated. Ras-GTPase activating protein and methyl-CpG-binding protein 2 were shown to be targets of *miR-132*. *miR-132* inhibition decreased SVP capacity to improve contractility, reparative angiogenesis, and interstitial fibrosis in infarcted hearts^[100].

Telocytes and miRNAs: Telocytes (TCs) are a novel type of interstitial cell recently discovered in the myocardium. Rat experimental MI was investigated using electron microscopy, immunocytochemistry and analysis of several pro-angiogenic miRNAs that provided evidence for TC involvement in neo-angiogenesis after MI. TCs contain measurable quantities of angiogenic miRNAs (*let-7e*, *miR-10a*, *miR-21*, *miR-27b*, *miR-100*, *miR-126-3p*, *miR-130a*, *miR-143*, *miR-155* and *miR-503*)^[101].

Bioinformatics analysis

Rationally designed bioinformatic analysis combined with experimental approaches to screen key therapeutic members of the IUPHAR database was conducted, following establishment of the whole genome protein interaction network and a comprehensive topological assessment. The number of validated and confidently predicted miRNAs regulating each gene encoding an ion channel or a gap junction protein was counted. Cx43 showed more intensive miRNA regulation compared with other ion channel and gap junction proteins^[102].

My-Inflamome: One of crucial processes in cardiac repair after MI is inflammation. In a study, a network has been established that enhances understanding of the inflammatory responses and its interaction network in human MI. The network is called My-Inflamome and it assembles protein interactions that are associated to inflammation and related to prognosis after MI. Classification models were established based on microarray data of blood samples from patients after MI with various disease consequences. Significant associations were experimentally verified. Different biological processes included in the heart repair are organized into modules. Small set of miRNAs is also included in modules that are significantly associated with transcriptional regulation^[103].

My-DTome: Another computational approach has been performed. It is based on different drug and protein interaction and it is called My-DTome (it is assembling the MI drug-target). It is also consisted of modules, which are related to the important molecular processes and pathways and to potential therapeutic approaches in MI that might be miRNAs-regulated. Non-cardiovascular drugs may also possess the cardiovascular effects and this systemic insight was established. This network might represent the basis for an investigation of new multidrug treatment and new targets MI^[104].

Polymorphisms in miRNA binding sites

After searching across dbSNP and TargetScan, 10 SNPs in

potential miRNA binding sites of 8 RAAS-related genes were identified and genotyped for risk for MI and blood pressure. It was found that nine SNPs in seven genes were prevalent. Of the nine SNPs, four in three genes were associated with blood pressure. The rare allele of the mineralocorticoid receptor (NR3C2) SNP rs5534 was associated with a twofold increased risk of MI in men younger than 50 years of age. The reduction in miR-induced repression of gene expression was demonstrated^[105].

CONCLUSION

In recent years miRNAs have been recognized as promising therapeutic, diagnostic and prognostic factors in the field of cardiovascular diseases. The usefulness of circulating miRNAs in the diagnosis and prognosis of MI has been established through numerous studies. Moreover, the therapeutic potential of miRNA has been established, especially in field of stem cell research. Heart tissue expression patterns examined in numerous experimental animals still need to be confirmed on human MI. Much more work is necessary before establishing routine use of miRNAs in clinical diagnosis, prognosis and therapy; however, the current findings are encouraging.

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Ventricular tachycardia mapping and ablation in arrhythmogenic right ventricular cardiomyopathy/dysplasia: Lessons Learned

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has allowed clinician scientists to better characterize the arrhythmia mechanism and develop the necessary strategies to perform successful catheter ablation. Early in this experience, catheter ablation was considered a limited and largely unsuccessful treatment for patients experiencing painful and recurrent defibrillator therapy. Through our increased understanding of the disease process, catheter ablation has evolved to become an effective and preferred therapy for a majority of these patients. Our understanding of the disease and necessary approaches to provide successful treatment continues to evolve as the clinical experience grows. This article will review these important insights from the electrophysiology laboratory and how application of this knowledge has facilitated the development of a methodical approach to successfully perform ventricular tachycardia ablation in patients with ARVC/D.

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Abstract

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is primarily believed to be an inherited cardiomyopathy that subsequently results in significant myocardial fibrosis. The arrhythmogenic consequences that result from the development of fibrosis are similar to other nonischemic cardiomyopathies, but the unique endocardial-epicardial disease process of ARVC/D requires a specialized approach for arrhythmia treatment in the electrophysiology laboratory. Although the association between ARVC/D and development of ventricular arrhythmias has become increasingly clear over the last 2 decades, our understanding of the arrhythmia mechanisms, underlying electrophysiologic substrate, and treatment strategies were significantly limited. Prospective studies performed in the electrophysiology laboratory allowed detailed characterization of the electrophysiologic and electroanatomic substrate underlying ventricular tachycardia in patients with ARVC/D. This

Key words: Arrhythmogenic right ventricular cardiomyopathy/dysplasia; Ventricular tachycardia; Mapping; Ablation

Core tip: This review article evaluates seminal insights derived from the electrophysiology laboratory and the lessons learned to develop a methodical approach that can be utilized to successfully perform ventricular tachycardia ablation in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia.

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INTRODUCTION

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a fascinating disease that continues to challenge clinicians and scientists since it was first described in 1728^[1]. Though several hypotheses have been proposed for the underlying cause of ARVC/D, it is primarily believed to be an inherited cardiomyopathy resulting from gene mutations that encode desmosomal proteins, the organelle responsible for cell-cell adhesion. Desmosomal dysfunction in patients with ARVC/D leads to inadequate cell adhesion and subsequent myocyte detachment and apoptosis^[2,3]. The accumulation of fibrous and adipose tissue predominantly affects the right ventricular free wall and typically extends inward from the epicardium toward the endocardial surface^[4,5]. Although this underlying process of ventricular scarring is unique to ARVC/D, the arrhythmogenic consequences that result from the development of fibrosis are similar to other nonischemic cardiomyopathies. The extensive right ventricle (RV) fibrosis results in inhomogeneous conduction with slow and discontinuous electrical propagation in sinus rhythm that serves as the substrate for ventricular arrhythmias. Although the association between ARVC/D and the subsequent development of ventricular arrhythmias had become increasingly clear following early clinical cohort reports, the characterization of arrhythmia mechanisms, the underlying electrophysiologic substrate, and treatment strategies were, until recently, poorly understood and limited.

Much of our understanding of the electrophysiologic and electroanatomic substrate underlying ventricular tachycardia (VT) in patients with ARVC/D was derived from studies performed within the electrophysiology laboratory. Through this experience, much has been learned about the arrhythmia mechanisms and strategies required to facilitate successful catheter ablation. The ability to localize and define the associated abnormalities essential for VT enhanced the effectiveness of catheter ablation procedures. What was once considered a treatment of last resort has now become the preferred therapy for most patients with documented ventricular arrhythmias. In addition, assessment of the anatomic substrate during electrophysiology procedures has shed important light on controversies pertaining to disease pathogenesis.

This review article will evaluate these seminal insights derived from the EP lab and the lessons learned to develop a methodical approach that can be utilized to successfully perform VT ablation in patients with ARVC/D.

PATIENT SELECTION FOR CATHETER ABLATION

Patients are typically diagnosed with ARVC/D after clinical manifestation of signs or symptoms during the second to fifth decade of life. We recommend implantable cardioverter-defibrillator (ICD) implantation to a majority of patients due to the high incidence of ventricular

arrhythmias associated with the disease after a definitive diagnosis is made according to the task-force criteria guidelines^[6]. Although ICD therapy is routine, management of recurrent VT with frequent device therapy can be difficult. Antiarrhythmic medications are often poorly tolerated and may only provide incomplete VT control. Inadequate arrhythmia control and the use of multiple antiarrhythmic medications is particularly debilitating for these young, and often physically very active patients.

Although techniques used in catheter ablation of VT in patients with ARVC/D have evolved over the last decade, outcomes are still inconsistent, ranging from 50%-90%^[7]. This is likely the result of a number of different mapping and ablation strategies with variable endpoints, follow-up assessment, and operator experience^[8-13]. In our experience at the University of Pennsylvania, a comprehensive ablation strategy that targets both the endocardial and epicardial substrate with elimination of abnormal electrograms and all inducible VT provides long-term drug-free arrhythmia control in a large majority of patients. For this reason, we offer catheter ablation to all patients with recurrent VT refractory or intolerant to medical therapy.

INSIGHTS FROM ELECTROANATOMIC MAPPING: DEFINING THE ELECTROPHYSIOLOGIC AND ELECTROANATOMIC SUBSTRATE UNDERLYING VT IN ARVC/D

Endocardial substrate

Advances in 3D electroanatomic mapping enabled a more thorough understanding of the complex electrophysiologic substrate in patients with ARVC/D and VT. Abnormal RV endocardial regions can be localized with electroanatomic mapping by identifying regions of low bipolar RV endocardial voltage (< 1.5 mV) and long-duration, low-amplitude, fractionated potentials. These key areas identified have been correlated to relevant histopathologic findings (myocyte loss with fibrofatty replacement) and critical VT circuits confirming the involvement of these areas in the arrhythmogenic mechanism^[14]. The endocardial distribution of electroanatomic scar in patients with VT and ARVC/D typically extends from the tricuspid valve and/or the pulmonary valve to the RV free wall. Low-voltage abnormalities can also be found on the septal aspect of the perivalvular region(s), but typically does not include the RV apex (Figure 1)^[15].

Although ARVC/D is known to primarily involve the RV, involvement of the left ventricle (LV) is more frequent than previously recognized. LV abnormalities have been documented with electroanatomic mapping and typically involve the basal perivalvular region, which is characteristic of other non-infarct related cardiomyopathies (Figure 2)^[15]. Consideration of endocardial LV involvement is of particular importance if right bundle branch block VTs

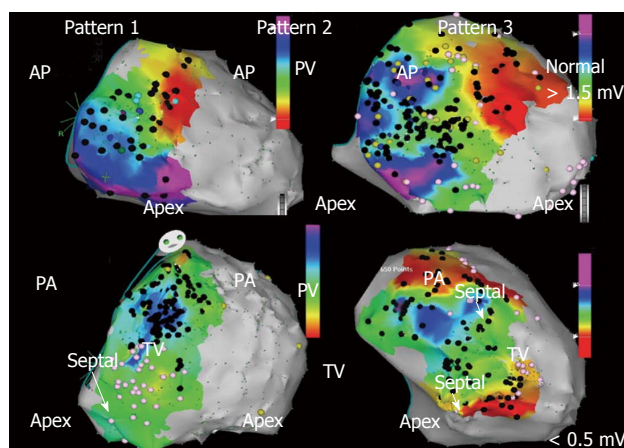


Figure 1 Bipolar right ventricle endocardial voltage maps demonstrating characteristic patterns of low voltage (< 1.5 mV) regions identified in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia and ventricular tachycardia in anterior and posterior views. Peritricuspid (pattern 1), peripulmonic (pattern 2), or more extensive involvement extending from both valvular regions (pattern 3) is shown. Distribution of abnormal electrograms is predominantly free wall. Right ventricle apex is spared, and septal involvement is frequently identified (arrows). Adapted from Marchlinski *et al.*^[15] with permission. AP: Anterior; PA: Posterior.

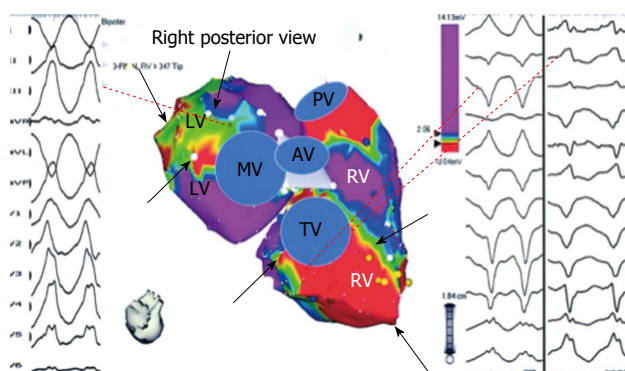


Figure 2 Bipolar right ventricle and left ventricle endocardial voltage maps highlighting location of abnormal endocardium and origin of ventricular tachycardia in a patient with right ventricle cardiomyopathy and ventricular tachycardia. Electroanatomic abnormalities include both the tricuspid and mitral valves from tricuspid and mitral valves (black arrows). Origin of ventricular tachycardia (VT) based on activation and pace mapping was perivalvular mitral for the RBBB VT and perivalvular tricuspid valve for LBBB VT (dashed lines). Adapted from Marchlinski *et al.*^[15] with permission. RV: Right ventricle; LV: Left ventricle.

with positive R waves in the precordial leads are seen as this suggests an LV VT exit site of interest.

Epicardial substrate

Despite periprocedural advances with irrigated ablation catheter technology and criteria to identify RV endocardial bipolar electroanatomic voltage abnormalities, the endocardial ablation approach provides only modest long-term arrhythmia freedom^[15]. The epicardial to endocardial scarring process associated with ARVC/D often results in a more extensive abnormal epicardial substrate that may not be amendable to endocardial ablation alone. Insights from percutaneous epicardial map-

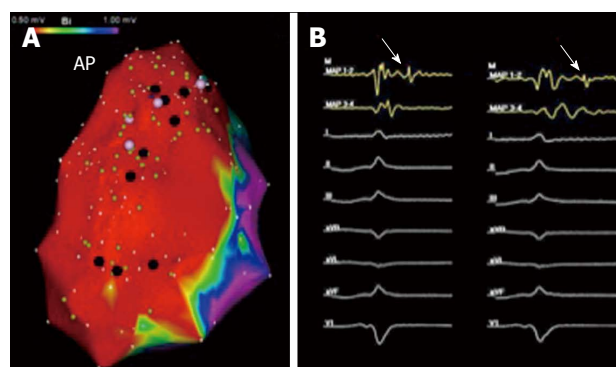


Figure 3 Epicardial right ventricle bipolar voltage map and isolated late potentials in sinus rhythm. A: Demonstrates significant epicardial bipolar voltage abnormalities (< 1.0 mV) over the right ventricle free wall. The black tags on the electroanatomical map represent areas of abnormal fractionated and/or late signals identified during sinus rhythm voltage mapping; B: Provides an example, as exhibited by the white arrows, of an isolated late potential. AP: Anterior.

ping and ablation procedures in patients with ARVC/D and VT have demonstrated the important role of the epicardium. Abnormal epicardial low-voltage areas are typically much larger than the corresponding endocardial region; with extensive networks of late activation and fractionated signals^[10,16]. Assessment of the epicardial voltage map should be performed with voltage threshold set to 1.0 mV to identify abnormalities consistent with scar as opposed to epicardial fat (Figure 3)^[17]. Due to the widespread extent of confluent scarring in these patients, it is very common to identify multiple VT circuits that may involve both endocardial and epicardial surfaces. In addition, the dense mid-myocardial/sub epicardial fibrosis can create an effective barrier for endocardial to epicardial spread of activation. The resultant layered and delayed activation of the epicardium from the edges of the scar creates the milieu for an isolated VT circuit entirely confined to the epicardium and requiring epicardial access and direct ablation for elimination (Figure 4)^[18]. In patients that have failed endocardial ablation, repeat ablation targeting the epicardial circuits was associated with superior long-term success rates^[10]. For these reasons, the operator should always anticipate a high likelihood of needing epicardial access for mapping and ablation to achieve a successful outcome.

Although identification of abnormal epicardial substrate is best achieved through a percutaneous pericardial puncture, analysis of unipolar endocardial voltage maps with the associated larger field-of-view, provides information pertaining to the degree of epicardial abnormality present. Areas of unipolar voltage < 5.5 mV are associated with epicardial abnormalities. Unipolar voltage abnormalities identified during RV endocardial mapping that far exceed the bipolar endocardial substrate is highly suggestive of a more extensive epicardial > endocardial substrate that is consistent with the ARVC/D substrate in patients with VT (Figure 5). Additional clues to the requirement for epicardial mapping and ablation include surface ECG morphologies of VT suggesting epicardial exits (QS complex in the inferior leads and/or right pre-

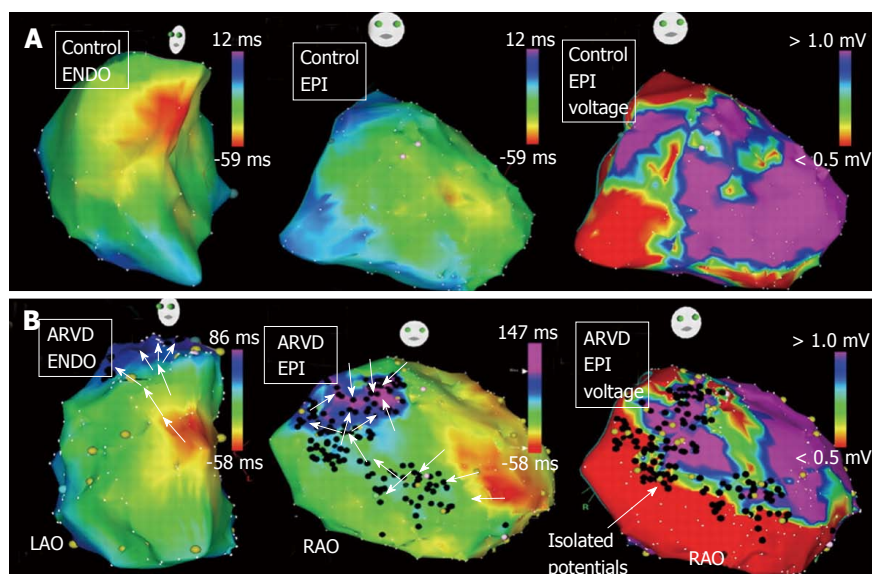


Figure 4 Right ventricle endocardial and epicardial activation maps and epicardial bipolar voltage maps of a control patient (A) and a patient with arrhythmogenic right ventricular cardiomyopathy/dysplasia (B) are shown. A: From control patient demonstrates continuous and rapid activation from the anteroseptal region toward the infundibulum and tricuspid annulus. The endocardial (not shown) and epicardial voltage map did not reveal any late potential or substantive voltage abnormalities; B: From patient with ARVC/D demonstrates significant epicardial scarring with epiendo isolated late potentials (black tags) on the bipolar voltage map. The activation wavefront is significantly delayed into the scar due to the extensive epicardial disease. Adapted from Haqqani *et al*^[18] with permission. RAO: Right anterior oblique; LAO: Left anterior oblique.

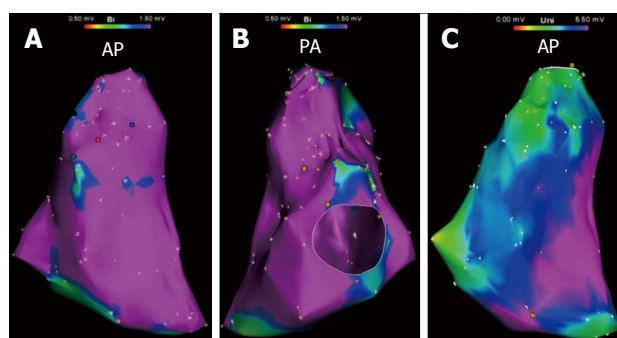


Figure 5 Bipolar and unipolar endocardial right ventricle voltage maps in a patient with ventricular tachycardia in the setting of arrhythmogenic right ventricular cardiomyopathy/dysplasia. A and B: Demonstrate no substantial endocardial substrate on bipolar voltage map; C: Demonstrates a substantial area of unipolar voltage abnormality (< 5.5 mV) encompassing most of the right ventricle free wall in the same patient. AP: Anterior; PA: Posterior.

cordial leads), the presence of isolated epicardial scar on magnetic resonance or intracardiac echo imaging, and/or prior failed endocardial ablation^[16,19,20].

Disease progression

Although much has been learned about the process of fibrosis underlying ARVC/D, there continues to be significant phenotypic variability for reasons that have not been clearly elucidated. Of note, multiple genes that have been implicated in the disease and this may lead to marked variability of phenotypic expression. It is unclear if disease progression is the result of a continuously progressive degenerative process or rather periods of disease stability followed by serial deteriorations associated with a distinct triggering event. The belief that ARVC/D is a

degenerative disorder has notably influenced treatment plans, particularly referral for catheter ablation. The degenerative hypothesis has been used as an explanation of unfavorable outcomes, thus labeling catheter ablation as a limited therapeutic option for patients with ARVC/D and VT. We have demonstrated, utilizing detailed electroanatomic mapping, progressive RV dilatation in patients presenting for repeat ablation procedures, but with no or only minimal macroscopic scar progression in a majority of patients (Figure 6)^[21]. This data along with the favorable outcome following endocardial/epicardial ablation and the demonstrated complex relationship between various genetic components and possible environmental or acquired factors favors a disease etiology that is not a primary deteriorating process.

PROCEDURAL APPROACH-LESSONS LEARNED

Mapping and ablation

Detailed assessment of the endocardial and epicardial electroanatomic maps has provided the much-needed insights into the complex abnormal substrate in patients with ARVC/D and VT. The cornerstone of developing a successful ablation approach in these patients requires a thorough understanding of this underlying substrate, particularly recognizing the importance of the epicardium. Through this evolving process, we have developed a systematic approach to evaluating the substrate and performing catheter ablation in these patients, much of which is centered on important lessons learned from within the electrophysiology laboratory over the last 2 decades.

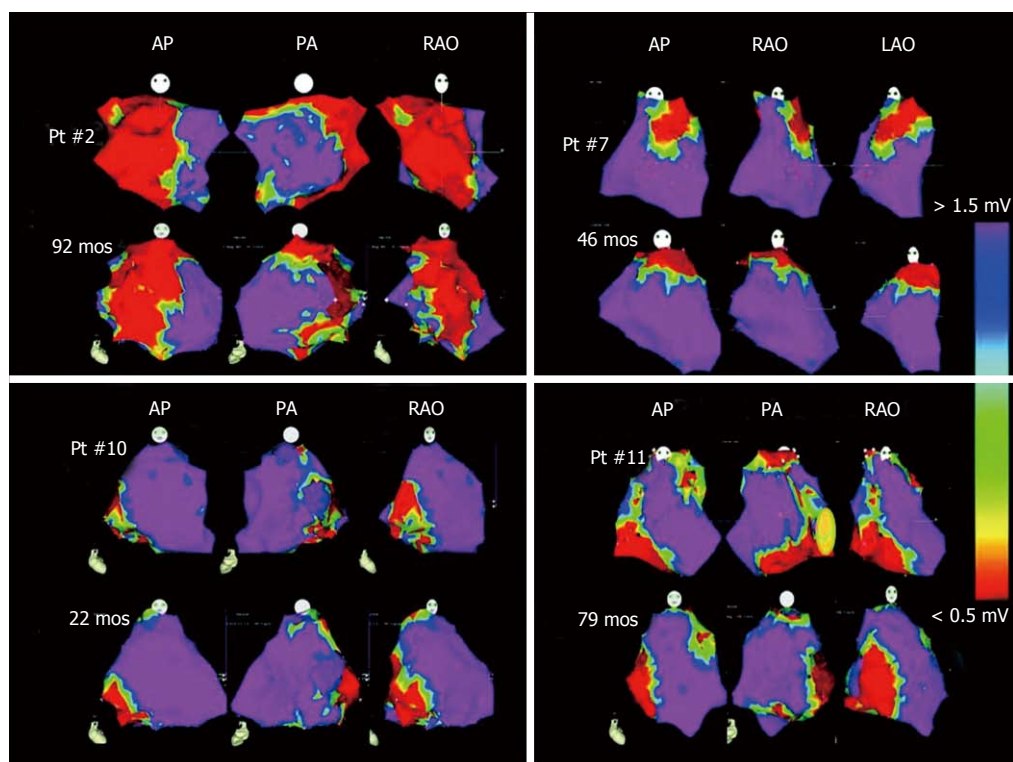


Figure 6 Right ventricle endocardial sinus rhythm bipolar voltage maps for 4 patients who did not develop scar progression over time. Each patient shows complementary views in the anterior (AP), right anterior oblique (RAO), and left anterior oblique (LAO) projections during initial and subsequent catheter ablation procedures. Normal voltage regions are represented in the purple regions and low voltage areas are represented in red. Adapted from Riley *et al.*^[21] with permission. PA: Posterior.

The general principles common to the ablation of all scar-related VT also apply in ARVC/D. However, in contrast to the post-infarction patient, the operator should anticipate a high likelihood of needing epicardial access for mapping and ablation to achieve a successful outcome for the reasons discussed. Evaluation in the EP laboratory typically begins with patients under conscious sedation to maximize the chances that induced VTs will be hemodynamically tolerated. A detailed RV endocardial voltage map is created in sinus rhythm using the standard 0.5-1.5 mV voltage cutoffs to define the endocardial substrate as previously discussed^[13,22]. Special attention is focused on the periannular area and any identified low-voltage areas to ensure adequate sampling has occurred^[23-25]. Occasionally, it can be technically challenging to perform catheter manipulation in the periannular tricuspid valve region. It is imperative to ensure adequate catheter contact during mapping to confirm low-voltage areas are from abnormal substrate and not inadequate catheter-tissue contact. This process can be facilitated by (1) using a sheath that extends transvenously to the tricuspid valve and provides stability; and/or (2) looping the mapping catheter in the RV to facilitate acquisition of detailed recording along the free wall adjacent to the annulus. Colored tags are placed on the electroanatomic map when fractionated signals and/or isolated late potentials are identified to keep track of their location^[26,27]. Pacemapping is performed at sites of interest with late potentials and other multicomponent electrograms and are carefully analyzed. A match of the

pacemap QRS morphology of the VT coupled with a long stimulus to QRS interval will identify additional sites of interest, which are given their own unique color tag. A sudden transition in paced QRS morphology coupled with changes in the stimulus to QRS interval may define anatomic boundaries of the isthmus or if a long stimulus to QRS is still identified a critical isthmus of conduction that will need to be tagged and ultimately targeted for ablation.

After completing the endocardial RV sinus rhythm substrate map and detailed pacemapping, programmed ventricular stimulation is performed. ICD electrograms are also recorded when VT is initiated. Induced VT ECG morphology and ICD electrograms are compared to previously captured clinical arrhythmias in addition to the pacemap morphologies that were obtained during sinus rhythm mapping. Assessment of ICD electrograms may be especially useful if clinical arrhythmia ECG tracings are unavailable^[28]. An endocardial ablation strategy is guided primarily by activation and entrainment mapping whenever possible of any hemodynamically tolerated VTs. It is not uncommon for unstable VT to be induced that is characterized by changes in morphology with any catheter manipulation or rates that results in hemodynamic instability. The VTs may not be amenable to localization utilizing conventional activation and entrainment mapping techniques. In these cases, ablation is guided by pacemapping and detailed substrate assessment. Ablation lesions are usually applied with an irrigated tip catheter

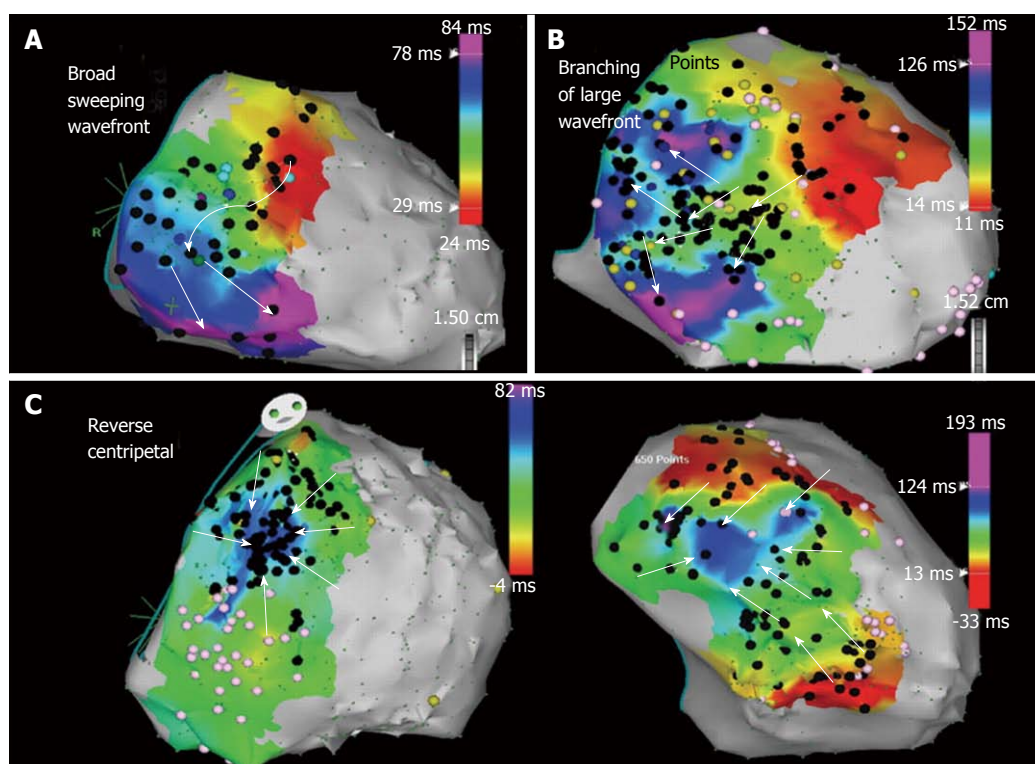


Figure 7 Epicardial right ventricle free wall activation maps illustrating propagation wavefront of epicardial isolated potentials in a patient with arrhythmogenic right ventricular cardiomyopathy/dysplasia. A: Right ventricle (RV) free wall activation via a broad wavefront progressing toward the inferior RV; B: A diverging pattern of activation, initially broad, but subsequently branching as it progresses through the scar; C: Reverse centripetal pattern with outside activation progressing inward with wavefront collision in the center of the scar. Adapted from Haqqani *et al*^[16] with permission.

for a minimum of 90 s. Power delivery begins at 20 Watts and is typically titrated to a maximum of 40 Watts to obtain a 12-15 Ohm impedance drop or approximately 10% decrease from the baseline impedance.

Any VT that can be mapped and successfully ablated from the endocardium is targeted initially. The use of irrigated RF energy delivery may eliminate all induced VTs with endocardial ablation alone^[13] though this is less likely in the context of ARVC/D than in ischemic VT. Epicardial mapping is required in cases when inducible VT is still present after endocardial ablation and should be planned for most patients.

When appropriate, the next step in the mapping and ablation procedure is to obtain intrapericardial access and perform epicardial mapping^[29]. We prefer to perform detailed endocardial mapping and ablation before proceeding with epicardial access. This has the advantage of eliminating many of the VTs and allowing for some VT control in most patients should the procedure be aborted due to difficulties or complications that may occur from the pericardial puncture.

Patients are usually placed under general anesthesia prior to performing the pericardial puncture, though we have performed the procedure under conscious sedation with remifentanyl and midazolam in select cases^[30]. A posterior access approach after subxiphoid entry with the Touhy needle is favored as patients with ARVC/D typically have RV dilatation that may increase the risk of RV perforation with an anterior approach (surgical backup

should always be readily available throughout the procedure). The posterior epicardial approach should begin just under the rib margin to minimize risk of liver laceration (Supplemental Video). After pericardial access is obtained, a detailed epicardial sinus rhythm voltage map is created in a similar fashion as described for the endocardium, but with voltage threshold set to 1.0 mV to identify abnormalities consistent with scar as previously described^[17]. Programmed stimulation is repeated and, if hemodynamically tolerated, the induced VTs are mapped using conventional activation and entrainment techniques. When this is not possible, as is frequently the case and further exacerbated by additional anesthetic vasodilatory effects, a substrate ablation strategy is required. An extensive epicardial lesion set is designed to incorporate sites of pacemap QRS matches to induced or clinical VT morphologies and all markedly abnormal multicomponent or late electrograms within the low voltage area that were identified during the detailed substrate map. On occasion we have been able to map the sequence of late potentials from earliest to latest originating at the scar border (Figures 4 and 7) and targeting the earliest late potential can effectively eliminate a large area of subsequent late potential activation. Occasionally, areas of abnormal electrograms can extend beyond the defined area of low voltage and these signals, late or split electrograms, should be targeted for ablation particularly if associated with a long stimulus to QRS and QRS morphology with pacing that matches the VT. These observations emphasized the crucial importance of pay-

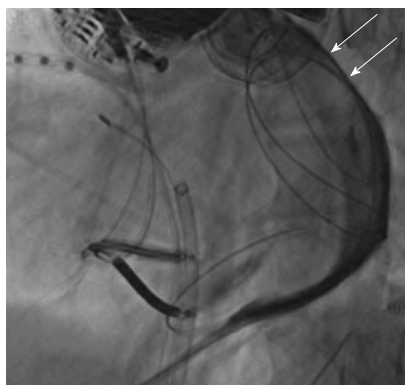


Figure 8 Fluoroscopic image in the left anterior oblique projection showing distribution of contrast restricted by pericardial compartmentalization from prior epicardial mapping and ablation. In this particular case, a deflectable catheter with a steerable sheath was not able to disrupt the adhesions and a more anterior epicardial access was required to bypass the area of compartmentalization to target the area of interest. Adapted from Tschabrunn *et al*^[33].

ing attention to electrogram characteristics as well as voltage when performing epicardial substrate mapping.

Special considerations pertaining to epicardial mapping and ablation

Coronary angiography is performed prior to epicardial ablation to ensure adequate distance between the coronary arteries (particularly the RV marginal branch of the right coronary artery) and ablation catheter. Phrenic nerve proximity to epicardial ablation sites is not an issue in ARVC/D cases although direct diaphragmatic stimulation may occur on the diaphragmatic surface of the RV. Epicardial ablation parameters for energy delivery are generally similar to the endocardium although the irrigation flow-rate is maintained at a lower rate (10-17 mL/min) to avoid unnecessary fluid accumulation with less concern about coagulum formation. Ideally, intracardiac echocardiography (ICE) is used to monitor lesion development and to assess for any complications throughout the procedure. Epicardial fat and thick fibrofatty replacement tissue can make it difficult to create lesions during epicardial ablation. It is important to ensure good contact at the catheter-tissue interface and optimal impedance drops for each lesion.

At the conclusion of the procedure, triamcinolone acetate (2 mg/kg) is injected into the pericardial space and allowed to disperse for 15 min before any suction is applied^[31]. This has been shown to minimize the severity of the pericardial inflammatory reaction following epicardial ablation lesion delivery and facilitates future percutaneous pericardial access if required^[32]. The pericardial drain is then attached to a passive suction device and removed the following morning after a transthoracic echocardiogram has confirmed no fluid accumulation overnight.

If a repeat procedure is required, the operator should be prepared to encounter pericardial adhesions during repeat epicardial mapping and ablation. These adhesions will be typically limited early after the initial procedure. The adhesions can usually be interrupted with the use

of a steerable flexed catheter tip coupled with a steerable sheath. Elimination of the adhesions will allow for detailed mapping^[32]. Careful monitoring for bleeding is important when disrupting the adhesions and is facilitated by utilizing ICE throughout this process. It is possible for dense adhesions to compartmentalize the epicardial surface and preclude access to the entire surface without re-accessing the pericardial space with a more anterior puncture (Figure 8)^[33]. When adhesions are found to be resistant to dissection, consideration should be made to have the patient undergo an open-chest procedure through a surgical incision, as the adhesions may not be safely lysed if a flexed catheter “u” shape cannot be advanced. A sternotomy may be required to permit dissection of matted pericardium that may not be amenable to catheter dissection.

Procedural endpoints

Our experience has consistently demonstrated that extensive endocardial and epicardial ablation is likely required to abolish all induced VTs. The primary procedure endpoint in these cases is both the elimination of a majority of abnormal electrograms and elimination of all induced VTs. Aggressive programmed stimulation should be performed as part of the evaluation of efficacy, including 2 stimulation sites, the introduction of up to triple extrastimuli, and the use of isoproterenol before the VT is described as non-inducible.

Non-invasive programmed stimulation through the ICD is performed 1-2 d after the ablation off antiarrhythmic drugs (AADs) to ensure continued non-inducibility^[34]. Induction of VT suggests the need for further ablation in order to achieve a favorable long-term antiarrhythmic drug-free outcome.

Whenever possible, AADs are discontinued and patients continue with beta-blocker therapy only. Approximately one third of our patients continue to be treated with low dose sotalol therapy, but the effort to discontinue amiodarone has been successful in all but one patient in our experience with 62 ARVC patients.

CONCLUSION

Ventricular tachycardia in ARVC/D patients can be a difficult clinical problem to manage. Antiarrhythmic medications are often ineffective or not tolerated leaving these young and active patients at high risk for recurrent ICD shocks. Much has been learned about the underlying arrhythmia substrate and the appropriate strategies required to facilitate successful catheter ablation. This comprehensive and extensive ablation strategy that targets both the endocardial and epicardial substrate with elimination of abnormal electrograms offers long-term, drug-free arrhythmia control in a majority of patients.

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Angiotensin II-related hypertension and eye diseases

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Core tip: Association between eye diseases and systemic hypertension has been revealed. The developments of some ocular diseases, as well as, alterations in the severity of these diseases have been associated with dysregulation of the ocular renin-angiotensin system and activation of the angiotensin type 1 receptor. In this paper we reviewed the importance of angiotensin II in the etiology of age-related macular degeneration and diabetic retinopathy, two ocular diseases that can rob people of their vision.

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Abstract

Systemic vascular disease, especially hypertension, has been suspected as a risk factor for some eye diseases including, diabetic retinopathy and age-related macular degeneration. Hypertension can contribute to chronic diseases by hemodynamic injury and/or cellular actions induced by hypertension-related hormones or growth factors. Among the most important is Angiotensin II (Ang II), which controls blood pressure and induces different cellular functions that may be dependent or independent of its effect on blood pressure. Importantly, as is true for heart, kidney and other organs, the renin-angiotensin system (RAS) is present in the eye. So, even in the absence of hypertension, local production of Ang II could be involved in eye diseases. The goal of this manuscript is to review the most relevant scientific evidence supporting the role of the RAS activation, in the development of age-related macular degeneration and diabetic retinopathy, and highlight the importance of Ang II in the etiology of these diseases.

INTRODUCTION

Knowledge of the renin-angiotensin system (RAS) has advanced remarkably over recent years from that of a classical endocrine system that explained homeostasis for maintenance of circulating intravascular volume and thereby restoration of arterial pressure to a newer concept including a number of local RASs that operate independently within several organs^[1-5], including the eye^[6,7].

Angiotensin II (Ang II), a hormone that raises blood pressure, is derived either from the circulation or from local production. Ang II causes vasoconstriction, sympathetic nervous stimulation, release of aldosterone, and renal actions which contribute to control the blood pressure^[8]. The effects of Ang II provoke different responses in tissue, which are mostly mediated *via* the Ang II type 1 receptor (AT1R). According to previous studies, the systemic RAS is not supposed to be directly accountable for the increase in blood pressure, it appears to be that

Table 1 Presence of renin-angiotensin system components in the eye

RAS molecule	Eye part	Species	Ref.
Prorenin	Retina	Human	Sramek <i>et al</i> ^[207] , 1988
	Ciliary body	Human	Danser <i>et al</i> ^[33] , 1989
	Vitreous body	Human	Danser <i>et al</i> ^[33] , 1989
Retina	Retina	Human, rabbit	Danser <i>et al</i> ^[33] , 1989
	Ciliary body	Rabbit	Wagner <i>et al</i> ^[19] , 1996
	Choroid	Human, Rabbit	Ramirez <i>et al</i> ^[208] , 1996
	Iris	Rabbit	Ramirez <i>et al</i> ^[208] , 1996
	Vitreous	Human, rabbit	Ramirez <i>et al</i> ^[208] , 1996
	Aqueous humor	Rabbit	Ramirez <i>et al</i> ^[208] , 1996
	Retina	Human, rabbit	Sramek <i>et al</i> ^[209] , 1992
Angiotensinogen	Ciliary body	Human, rabbit	Ramirez <i>et al</i> ^[208] , 1996
	Choroid	Human, rabbit	Wagner <i>et al</i> ^[19] , 1996
	Iris	Human, rabbit	Wagner <i>et al</i> ^[19] , 1996
	Vitreous	Human, rabbit	Wagner <i>et al</i> ^[19] , 1996
	Aqueous humor	Rabbit	
	Retina	Dog, monkey, human	Vita <i>et al</i> ^[210] , 1981
	Ciliary body	Rabbit, porcine	Weinreb <i>et al</i> ^[211] , 1985
ACE1	Choroid	Human, rabbit, porcine	Immonen <i>et al</i> ^[212] , 1987
		Dog, monkey, human	Ramirez <i>et al</i> ^[208] , 1996
		Rabbit, porcine	Wagner <i>et al</i> ^[19] , 1996
	Sclera	Dog, monkey	Shiota <i>et al</i> ^[213] , 1997
	Iris	Rabbit, porcine	Geng <i>et al</i> ^[214] , 2003
	Cornea	Human	Savaskan <i>et al</i> ^[16] , 2004
	Vitreous	Dog, monkey, rabbit	Savaskan <i>et al</i> ^[16] , 2004
	Aqueous humor	Human, dog, monkey, rabbit	Savaskan <i>et al</i> ^[16] , 2004
	Tear fluid	Human, rabbit	Savaskan <i>et al</i> ^[16] , 2004
	Retina	Rodent	Tikellis <i>et al</i> ^[215] , 2004
		Human	Senanayake <i>et al</i> ^[17] , 2007
ACE2			
Chymase	Choroid	Dog	Shiota <i>et al</i> ^[213] , 1997
	Sclera	Dog	Maruichi <i>et al</i> ^[216] , 2004
	Vitreous body	Human	
AT1R	Retina	Human	Savaskan <i>et al</i> ^[16] , 2004
	Cornea	Human	Senanayake <i>et al</i> ^[17] , 2007
	RPE	Human	Striker <i>et al</i> ^[18] , 2008
AT2R		Rodent	Praddaude <i>et al</i> ^[104] , 2009
	Retina	Human	Senanayake <i>et al</i> ^[17] , 2007
	RPE	Human	Striker <i>et al</i> ^[18] , 2008
		Rodent	Praddaude <i>et al</i> ^[104] , 2009
Ang I	Retina	Porcine	Danser <i>et al</i> ^[22] , 1994
	Choroid	Porcine	
	Vitreous body	Porcine, human	
Ang II	Aqueous humor	Human	
	Retina	Human, porcine, rabbit	Danser <i>et al</i> ^[22] , 1994
	Ciliary body	Human, rabbit	Ramirez <i>et al</i> ^[208] , 1996
	Choroid	Porcine, human, rabbit	Savaskan <i>et al</i> ^[16] , 2004
	Iris	Rabbit	Senanayake <i>et al</i> ^[17] , 2007
	Cornea	Human	
	Vitreous body	Porcine, human, rabbit	
	Aqueous humor	Human, rabbit	
Ang 1-7	RPE	Rodent	Praddaude <i>et al</i> ^[104] , 2009
	Retina	Human	Senanayake <i>et al</i> ^[17] , 2007

Ang: Angiotensin; RAS: Renin-angiotensin system; AT1R: Angiotensin II type 1 receptor; ACE1: Angiotensin-converting-enzyme 1.

the blood pressure and local blood flow (BF) adjustment are due to the local RAS^[9]. Ang II directly or indirectly also promotes apoptosis, hypertrophy, neovascularization, inflammation and fibrosis *via* AT1R activation^[10-13].

Ophthalmic literature concerning the RAS started in 1977 with a study by Igić *et al*^[14] on the detection of angiotensin-converting-enzyme (ACE) activity in homogenates of the retina. Since then, and as shown in Table 1, the presence of all constituent of the RAS has been confirmed in different parts of the eye (Figure 1), where

the mediators of the RAS are locally released, conferring the molecular basis for a biological function of these mediators in the eye^[15-18]. However, the origin of intraocular mediators such as Ang II and renin has been debated. Local synthesis of both renin and ACE has been suggested in the retina of rats^[19]. In this way, the secretion of renin by retinal pigment epithelium (RPE) to the retinal side was demonstrated by Milenkovic *et al*^[20] (2010). It has been also suggested that Ang I, Ang II, and angiotensinogen are not able to cross the barriers between eye

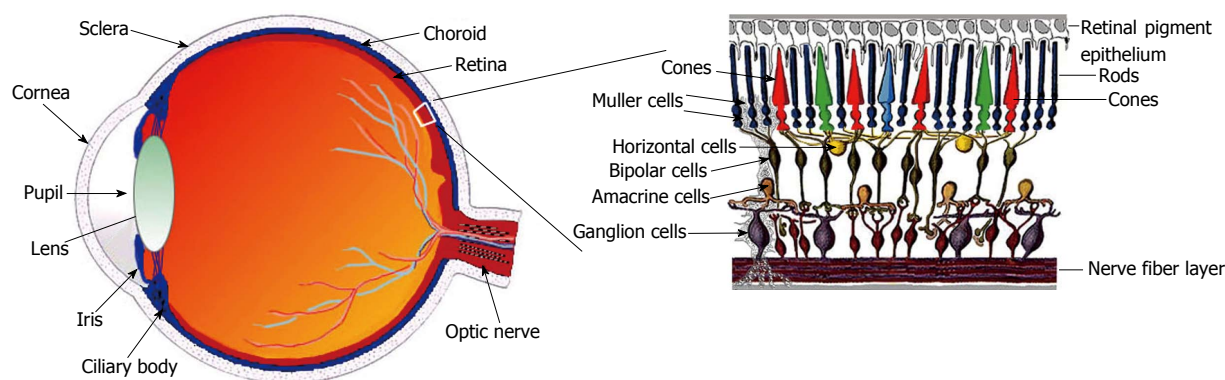


Figure 1 A drawing of a section through the human eye with a schematic enlargement of the retina [Helga Kolb from AMER Sci (2003)].

and circulating blood^[21,22]. On the other hand, the presence of an ocular local production of Ang II has been indicated^[22,23]. As a result, increased local or tissue Ang II formation in the retina in the absence of elevated circulating Ang II may indeed be deleterious.

The RPE, a cell layer between the neurosensory retina and choroid, nourishes retinal visual cells and forms part of the blood-retinal barrier, therefore, playing a central role in maintaining retinal function. For example, the presence of the AT1R in the RPE basolateral membrane^[20], indicates that the systemic RAS is a part of that retinal function signaling. Interestingly, by using electroretinography, it was previously demonstrated that regulation of the systemic RAS changes the neuro-sensory retina activity^[24-26]. Furthermore, plasma Ang II cannot pass into the eye^[7], and modifications of the renin expression in the RPE by regulators of the systemic RAS alter, have been observed^[24]. Overall, these data lead to think the systemic RAS credits the presence of an intraocular RAS through the RPE.

The presence of the most important RAS components in the retina and the Ang II actions observed in the eye (Surveying PubMed for eye, ocular, or retina, and Ang yields 734 citations dating back to 1963), imply an important role of RAS in the eye. However, its exact role, remains inadequately recognized. Of special focus are the components of the RAS and its receptors in the retina, as the RAS is increasingly recognized as a mediator of the pathogenesis of ocular diseases such as age-related macular degeneration (AMD) and diabetic retinopathy (DR)^[27-36], which are two major causes of severe vision loss and blindness. Therefore, in this manuscript we review the most relevant scientific evidence supporting the function of the RAS activation, in the development of AMD and DR, and highlight the importance of Ang II in the etiology of these two ocular diseases.

RETINAL MICROVASCULATURE: MODULATION BY ANG II

Given that vascular pathology in the retina is an important contributor of vision loss, the greatest research examining retinopathy and the possible role played by the RAS

has been focused on the microvasculature. The circulatory system of the retina supplies oxygen and nutrients to retinal tissue, which is essential for a correct function.

The retina circulation essentially comprises two parts: (1) a retinal circulation without autonomic innervation; and (2) a choroidal vasculature with autonomic innervations^[37]. Evidence is accumulating that the retinal microvasculature is an interactive complex that includes a network of capillaries and a tertiary arteriole that links the capillaries with a secondary arteriole (Figure 2). The capillary is formed by an uninterrupted endothelium and inner pericytes^[38]. Both endothelial cells and pericytes are directly communicated and share a common basement membrane^[39]. It was previously demonstrated that contraction and relaxation of pericytes leads to alterations in the capillary lumen, which could regulate local perfusion^[40-45]. Moreover, evidence suggests that a capillary network including pre-capillary at the tertiary arteriole form a working unit which is able to control local perfusion within the retinal vessels^[39,46,47].

The retina tends to keep its BF constant through an autoregulatory response that is intrinsic^[48,49]. The autoregulation of the retinal microcirculation is evaluated by some methods, including changes in systemic blood pressure^[50]. The main regulators of BF are the vascular pericytes^[51,52], endothelium cells and the neural and glial cells^[53]. One of the most important peptides playing a crucial role in the regulation of vasculature tone is Ang II^[54-58]. For instance, it has been demonstrated that Ang II induces retinal endothelial cells apoptosis^[59] and constriction of pericytes^[60-63], therefore, decreasing the mean retinal arterioles and capillaries diameter, which leads to BF reduction^[51,52].

Modifications in the retinal BF has been observed in some eye disorders. For example disturbances in the ocular circulation have been reported in AMD^[31-33], supporting the presence of hemodynamic abnormalities in this disease. AMD is the main cause of severe visual loss and legal blindness in elderly. There are three stages of AMD: (1) early AMD, which is diagnosed by the presence of medium-sized drusen; (2) intermediate AMD, characterized by the presence of large drusen and/or pigment changes in the retina; and (3) late AMD, in which in addition to drusen, there is damage of the macula with severe

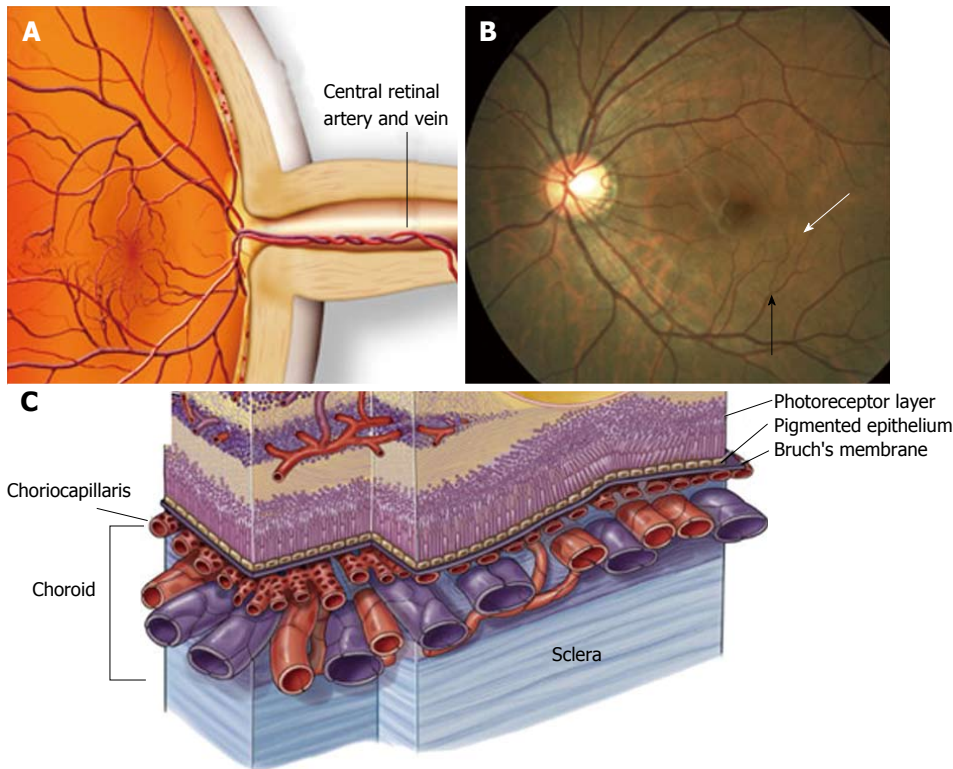


Figure 2 Anatomy of ocular circulation. A: Central retinal artery and vein respectively; B: Arteriole (black arrowhead); capillaries (white arrowhead); C: Choroidal vasculature (Anand-Apte, Hollyfield, Academic Press, Elsevier Books, 2009; 9-15).

vision loss^[64]. Both local ocular and systemic vascular risk factors, such as systemic hypertension seem to be connected with the etiology of AMD. A relationship between AMD and modifications in the eye circulation was previously reported^[27,29,65-72] and numerous studies have proposed a decrease in the vascularity of the choroid^[73-75], reinforcing the existence of hemodynamic abnormalities in this disease. The relationship between impaired choroidal perfusion, reduced choroidal BF and clinical manifestations of AMD has been recently reported by previous studies^[70,71,75-79].

Association between AMD and systemic hypertension has been studied by many epidemiological studies^[80-84]. The Macular Photocoagulation Study has demonstrated that patients with both, AMD and hypertension responded less to laser photocoagulation treatment than patients with only AMD^[85]. These observations, suggested that hypertension could have a harmful effect on the stages of AMD. A decrease in the choroidal BF in individuals with hypertension versus those without was previously reported^[31,32]. These authors, also showed that this reduction becomes more marked with increasing AMD severity^[31,32]. Therefore, the observed decrease in choroidal BF in AMD patients with hypertension suggests the implication of an ischemic mechanism in the etiology of AMD.

ANG II -RELATED HYPERTENSION IN THE PATHOGENESIS OF AMD

AMD is a slow progressing disease that can rob people

of their vision. This ocular disease is a public health problem that will remain a major threat to vision.

There are two forms of AMD; early (dry) AMD and late (wet) form. Wet AMD is always preceded by early disease, and in about one-third of cases dry AMD can lead to wet macular degeneration which progresses much more rapidly and leads to greater loss of central vision. Death of photoreceptors is the ultimate cause of vision loss. However, the initial cellular target of this disease is the RPE, its extracellular matrix, and the subjacent vascular bed (called choriocapillaris; Figure 2C), the blood supply for the outer retina.

Dry AMD is characterized by the accumulation of debris and other lipid rich extracellular deposits in form of drusen under the RPE and within Bruch's membrane (BrM) (Figure 3B)^[86,87]. During aging, deposits initially accumulate between the RPE and its basement membrane (called BLD), but progression into AMD requires additional deposit formation within BrM, (called BLiD and "nodular" drusen). These are yellowish lesions that can be seen in the macula at the earliest stages of dry AMD. A finding in dry AMD that represents disease progression and can be used as a surrogate endpoint is the presence, size, and appearance of drusen. Over time, these drusen enlarge, coalesce, become pigmented, and eventually can disappear when they progress to the late form of AMD. We observed that when drusen go away, there are three possible outcomes; formation of geographic atrophy, formation of abnormal blood vessels known as wet AMD or choroidal neovascularization (CNV) (Figure 3C), or disappearance of drusen without any significant

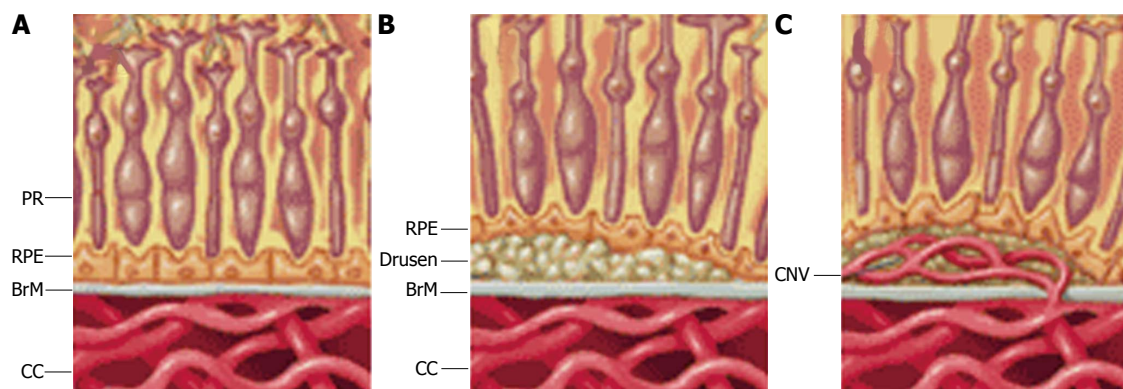


Figure 3 The pathologic changes to the retina and choroidal blood vessels typical of dry and early wet age-related macular degeneration respectively. A: Control; B: Early age-related macular degeneration (AMD); C: Wet AMD. PR: Photoreceptors; RPE: Retinal pigment epithelium; BrM: Bruch's membrane; CC: Choriocapillaries; CNV: Choroidal neovascularization (provided by the OcuCure Therapeutics' website).

anatomic abnormality. The endpoint that represents the progression of the disease is the growth and enlargement rate of drusen^[88-90]. Wet AMD is always preceded by early disease.

Our understanding of this disease has increased; however, no one knows exactly what causes AMD. Age is the major factor determinant for developing AMD. However, it has been suggested that the disease results from some interactions between different issues: genetic susceptibility, environmental factors and systemic health co-factors^[91-95]. Because the increasing frequency of hypertension, the RAS is of special interest among these systemic health co-factors. In this context, epidemiological demonstrated an association between hypertension and incidence of drusen^[28] and with wet AMD development^[29,96-98]. Exciting findings which showed a strong link between hypertension and progression of early AMD to the wet form were recently published^[99]. However, the mechanism(s) by which hypertension contribute to the progression from early form to CNV was not elucidated. In recent years, evidence has revealed that Ang II, AT1R signaling, and prorenin, may play a significant role in the mentioned pathologic processes^[100-104]. Moreover, recent studies revealed the participation of AT2R, Ang I and Ang 1-7^[24]. Consequently, investigation of the local RAS in the retina will allow find out new approach for the development of new treatments.

Dry (early) AMD

As mentioned previously, RPE-derived debris and other debris accumulated between the RPE and within BrM is a very well-known histopathologic sign of the dry AMD^[105-108]. Studies in eyes from AMD patient found out deposits of RPE-derived debris within BrM^[109]. Nevertheless, the mechanism(s) by which the debris accumulate were not studied. Based in the idea that a relationship between matrix metalloproteinases (MMPs) and inhibitors of matrix metalloproteinases and development of dry AMD exists. We proposed that the evolution of the sub-RPE deposits into BrM necessitates breakdown of the RPE basement membrane's components by diges-

tion or degradation of these compounds (*i.e.*, type IV and I collagens and laminin)^[110,111], and that ECM turnover up-regulation through activation of MMP-2 and MMP-14 is required for the interruption of these physical barriers. We evaluated the regulatory effects of Ang II and prorenin-activated prorenin receptor (PRR) on the MMP-2 and basement membrane component proteins, in the RPE. The objective of our work was to describe the expression and function of Ang II receptors in the RPE and at explore the contribution of this hormone and PRR in the etiology of dry AMD. Mice were rendered hypertensive either by exogenous administration of Ang II or by using a model of experimental renovascular hypertension (1K1C). Measurements of systolic blood pressure (BP) revealed a progressive increase during Ang II infusion period reaching a peak value on day 14 and remaining at plateau through day 30. However, after 24 h of exposure to Ang II, BP was not modified. Similarly, BP was significantly higher in 1K1C mice compared with the corresponding sham-operated group. No significant differences in BP were observed between control and sham-operated groups. Treatment using Ang II in combination with angiotensin receptors blockers showed that the AT1R blocker eliminated the modifications in the BP due to Ang II. However, the AT2R blocker did not alter the effect of Ang II on systolic BP, demonstrating, that the effect on BP caused by Ang II was AT1R mediated^[104,112].

Our study in human and mouse also confirmed that both ATRs were expressed and upregulated by Ang II in the RPE and showed that the activation of the AT1R by Ang II increased the intracellular calcium levels^[18,105]. These results clearly evidenced the functionality of the RPE's AT1R, which could be coupled to the phospholipase C-pathway. In contrast, activation of the AT2R by Ang II did not mobilize intracellular calcium. AT2R could be coupled to the cytosolic phospholipase A2 and not to the PLC pathway as shown for other tissues^[113]. Consequently, regulation of the AT2R transduction pathway is a possibility to be explored.

Ang II also up-regulated the activity of MMP-2,

MMP-14, and basigin (also known as extracellular matrix metalloproteinase inducer or cluster of differentiation 147) as well as digestion of type IV collagen^[18,104,112]. The Ang II observed effects were blocked by the AT1R antagonist candesartan. *In vivo*, the Ang II-derived decrease in collagen IV was AT1R/AT2R mediated, implying a synergistic effect. Therefore, Ang II through MMP-2, MMP-14, and basigin regulation could stimulate RPE basement membrane breakdown allowing the migration of BLD and buildup of BLiD deposits or drusen.

It is important to note that the majority of intracellular effects of Ang II in most tissues are MAPKs mediated. MAPKs are a group of serine/threonine kinases^[114-116] which can be divided into three major groups: ERK, p38, and Jun N-terminus kinase (JNK) and participate in a wide array of cellular responses including proliferation, differentiation, migration, and stress responses among others^[117-120]. We explored the involvement of MAPK as intracellular modulator of Ang II-induced up-regulation of MMPs in the RPE. Our study showed that Ang II-induced increase in MMP-2 activity is mediated by Erk(1/2) and p38 MAPK in the human RPE cell line ARPE-19. We also demonstrate that Ang II increased the expression of MMP-14, MMP-2 activity major regulator, in an Erk(1/2) and p38 MAPK-dependent way while basigin does not appear to be involved in RPE cells. In addition, we reported that Erk/p38 MAP kinase signaling pathway is AT1R mediated, which could be an important mechanism by which Ang II up-regulates MMPs in RPE cells. Moreover, we show that RPE from mice exposed to Ang II for 4 wk showed increased MMP-14 and basigin protein expression as well as increased phosphorylated Erk(1/2), p38, and JNK MAPK. The increase in MMP-14 protein expression and activation of Erk(1/2), p38, and JNK MAPK were AT1 receptor-mediated, whereas the increase in basigin expression increase was mediated by AT2 receptor^[112]. Blockade of extracellular signal-regulated kinases or p38 MAPK abolished the up-regulation of MMPs in RPE cells^[112]. Given that MMP-14 and basigin are major inducers of MMP-2, our results lead us to speculate that MMP-14 and basigin might regulate Ang II-induced MMP-2 activity through MAPKS- and AT1 receptor-dependent signaling pathways in the RPE. These original observations highlight the potential importance of this signaling pathway as a potential mediator of RPE response to Ang II-induced ECM dysregulation and disruption of the RPE basement membrane believed to be involved in sub-RPE deposits progression in the pathogenesis of AMD. Based on our observations, MAPKs inhibitors and AT1R blockers may prevent these changes in the ECM, which are essential in the development of early AMD.

We also provided evidence that activation of the PRR may be involved in ECM-remodeling through increase of collagen I^[121]. Interestingly, we confirmed that PRR and type I collagen were present in human retinas and that the expression of both proteins was higher in the RPE from dry AMD hypertensive donors (Figure 4), support-

ing our *in vitro* findings. Overall, our studies suggest a molecular mechanism by which hypertension may aggravate the pathology of dry AMD.

Even though dry AMD is not a retinal vascular pathology, we reviewed this form of the disease here because hypertension-related Ang II has been implicated in dry AMD pathogenesis^[28], and wet AMD is always preceded by the early form of the disease.

Wet AMD

As mentioned previously, about one-third of cases dry AMD can lead to wet macular degeneration which progresses much more rapidly and leads to loss of central vision. CNV is a retinal vasculature related pathology^[120] associated with several common retinal degenerative or inflammatory diseases^[87,120,122,123]. Inflammation and hypoxia are key cellular processes involved in the development of CNV^[17-25], in that choroidal monocytes processes, for example, have been noted to insert into BrM deposits suggesting that these sub-RPE deposits may generate inflammatory stimulus at the BrM and sub-RPE space. Macrophage infiltration to the damaged sites by chemotactic factors may be responsible for the production of inflammatory cytokines and angiogenic factors such as intercellular adhesion molecule 1 (ICAM-1) and monocyte chemoattractant protein-1 (MCP-1)^[124] and vascular endothelial growth factor (VEGF)^[125] which will ultimately contribute to induction and/or progression of CNV^[26-28]. Blockade of AT1R by systemic administration of telmisartan reduced CNV formation, macrophage infiltration and expression of VEGF, VEGF receptor-2 (VEGFR-1), ICAM-1 MCP-1 and interleukin 6 in eyes from a laser induced CNV mouse model of AMD^[125]. This suggests that AT1R mediated up-regulation of these molecules and mediators participate in the development of CNV.

Ang II has been shown to act as an indirect mitogenic agent for retinal vascular endothelial cells by increasing VEGFR-2 expression^[23] which could lead to formation of CNV. Blockade of AT1R signaling suppresses pathologic but not normal retinal neovascularization by inhibiting inflammatory processes^[34,116]. Additionally, it has been shown that excised choroidal neovascular membranes from patients with AMD express AT1R, AT2R and Ang II on the vascular endothelium^[126]. Similar findings were seen in the laser-induced mouse model of CNV^[126]. As noted above, formation of CNV was suppressed with the AT1R blocker telmisartan but not with an AT2R antagonist^[127]. In a laser induced model of CNV using AT1R knockout mice, the ACE inhibitor, imidapril, significantly reduced choroidal and retinal neovascularization in wild type mice to levels detected in laser treated AT1R KO mice^[128]. Additionally, in a rat model of laser-induced CNV, losartan was shown to inhibit the incidence of new vessel formation from 99.5% to 72.5%^[129].

Increasing evidence support the notion that increase in the production of chemokines happens in diseases related to an inflammatory component. Several of these chemokines are expressed in the RPE cells, including

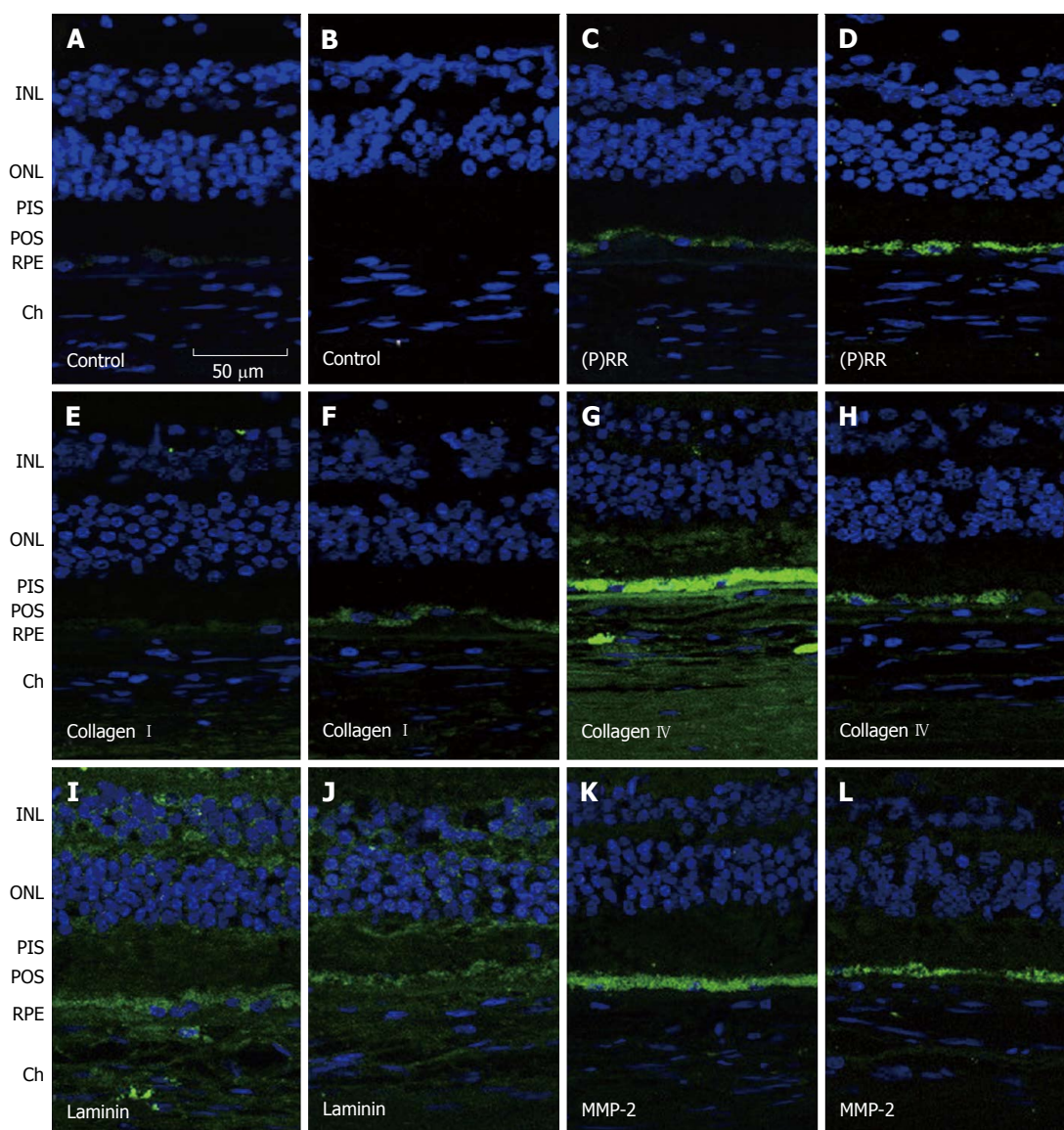


Figure 4 Representative immunofluorescent double staining of prorenin receptor, collagen types I and IV, laminin and matrix metalloproteinase-2 (green) and nuclei (bleu) in retina sections from human donor eyes with no known eye disease (B, D, F, H, J and L), and human donor eyes with dry age-related macular degeneration and hypertension (A, C, E, G, I and K)^[121]. Negative controls were generated by omission of the primary antibody (A and B). Sections were analyzed by using confocal microscopy (original magnification, $\times 40$). INL: Inner sections were analyzed with a confocal microscope at a magnification of $\times 40$. INL: Inner nuclear layer; ONL: Outer nuclear layer; MMP: Matrix metalloproteinase; PIS: Photoreceptor inner segments; POS: Photoreceptor outer segments; RPE: Retinal pigment epithelium; Ch: Choroid.

MCP-1^[29,30], which has been proposed to be implicated in the development of dry and wet AMD^[31-33]. During inflammatory responses, RPE cells have been shown to secrete MCP-1 toward the choroid, consequently, implying that RPE cells might induce recruitment of macrophage to the choroid^[34]. There is clear evidence for the role of MCP-1 in angiogenesis in several angiogenic-related disorders^[35-37]. Interestingly, expression of the recently discovered novel zinc finger protein MCP-1 induced protein (MCPIP) has been shown to induce tube formation in human umbilical vein endothelial cells^[38].

As mentioned previously, hypoxia, which was proposed to be one of the most significant driving forces for CNV formation^[130], is another key cellular process which stimulates the expression of VEGF in AMD. Angiogenic

factor expression occurring secondary to hypoxia is mediated by the family of transcription regulators known as hypoxia inducible factors (HIF). HIF-1 and -2 have been found to be expressed in human choroidal neovascular membranes^[131], and HIF-1 has been shown to upregulate expression of VEGF in RPE^[132,133]. Hypertension-associated Ang II is known to induce inflammation, macrophage infiltration, and angiogenesis by stimulating expression of MCP-1, HIF-1 and VEGF through the AT1R^[126,134-137]. Up-regulation of MCP-1 has been demonstrated in hypoxic animals^[138] and recently, it has been demonstrated that MCP-1 promotes angiogenesis *via* MCPIP, HIF-1 and VEGF induction^[139]. Interestingly, previous works also suggest that the BF in the choroidal and retinal is down-regulated in AMD hypertensive

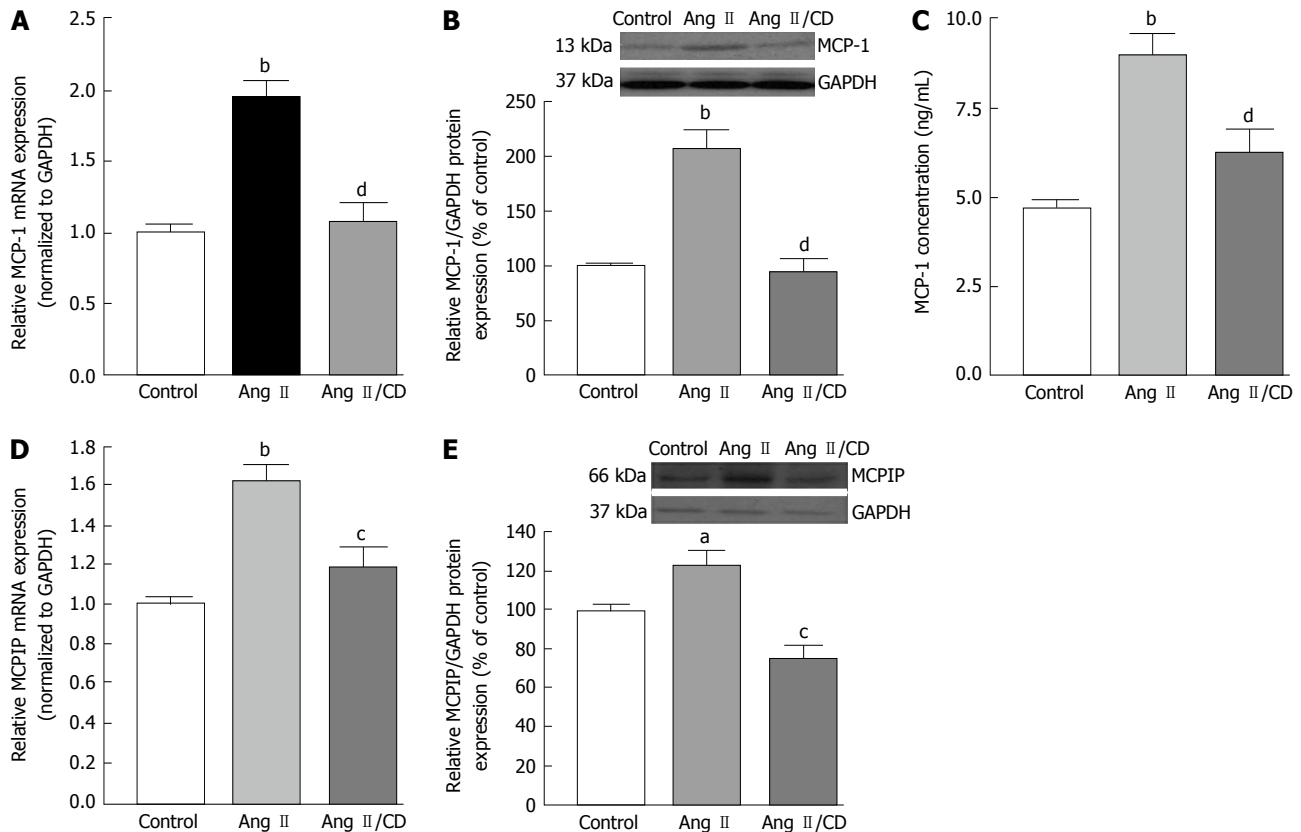


Figure 5 Hypertension-induced Angiotensin II up-regulated monocyte chemoattractant protein-1 and monocyte chemoattractant protein-1 induced protein expression through AT1R activation in retinal pigmented epithelium-choroid^[140]. C57BL 6 mice were treated with saline (1), Ang II (2), and Ang II in combination with candesartan (10 mg/kg per day) (3). Blood pressure was recorded before and after treatment. After 30 d of treatment, animals were sacrificed and eyes enucleated and collected for microdissection of retinal pigmented epithelium-choroid. Monocyte chemoattractant protein-1 (MCP-1) and MCP-1 induced protein (MCP-1P) proteins were analyzed by real-time PCR and Western blot. MCP-1 and MCP-1P mRNA expression by real-time PCR (A and D), protein expression by Western blot (B and E), and MCP-1 protein secretion by ELISA (C). GAPDH was used as control. Data are expressed as mean \pm SE ($n = 3$). ^a $P < 0.05$, ^b $P < 0.01$ vs control; ^c $P < 0.05$, ^d $P < 0.01$ vs Ang II-treated animals. CD: Candesartan. Ang: Angiotensin; PCR: Polymerase chain reaction; GAPDH: Glyceraldehyde 3-phosphate dehydrogenase; ELISA: Enzyme-linked immuno assay.

patients^[31,32], which leads to think about the possibility that an ischaemic/hypoxia mechanism plays a role in the CNV development. Given that a positive correlation between elevated levels of circulating MCP-1 and hypertension has been previously shown, we studied whether hypertension-induced Ang II influences the development of CNV and characterized the role played by MCP-1/MCP-1P in this event. We addressed this by setting goals of understanding the mechanisms underlying the interactions between the RPE, choroidal microvascular endothelial cells (cEC) and Ang II which may contribute to CNV development in hypertensive dry AMD patients.

Our results indicated that hypertension-induced Ang II increases MCP-1 and MCP-1P expression in mouse RPE-choroid through AT1 receptor. *In vitro*, MCP-1 and MCP-1P expression was up-regulated by Ang II in RPE cells. Moreover, MCP-1 induced expression of MCP-1P in RPE cells, which led to cEC tube formation (Figures 5-7) (Marin-Castano *et al.*^[140] IOVS 2013; ARVO E-Abstract 6089). Therefore, our data support the hypothesis that Ang II, through MCP-1/MCP-1P may contribute to CNV, proposing a possible mechanism linking hypertension and CNV, which can provide new targets for more effective early preventive and novel therapeutic interventions.

DR AND THE RAS

The incidence of DR is alarming. A recent study emphasizes that 93 million people have DR, and that about 17 million have the blinding form of the disease^[141]. Patients with type 1 or type 2 diabetes are at risk for the development of DR. The longer a person has diabetes, the more likely they are to develop DR^[142]. DR is classified into two types: (1) non-proliferative DR (NPDR), the early state of the disease. In NPDR, the blood vessels in the retina are weakened causing tiny bulges called microaneurysms. The microaneurysms may leak fluid into the retina, which may lead to swelling of the macula; and (2) proliferative DR (PDR), which is the more advanced form of the disease. At this stage, the retina becomes oxygen deprived. New blood vessels can start to grow in the retina and into the vitreous causing clouding vision. If left untreated, PDR can cause severe vision loss and even blindness^[143]. The progression to PDR looks like to be a result of tissue ischemia and the consequent increase in the production of angiogenic growth factors such as VEGF.

The report that some components of the RAS are augmented in blood and eyes from DR patients^[46,144,145], suggests the RAS may be implicated in the pathogenesis

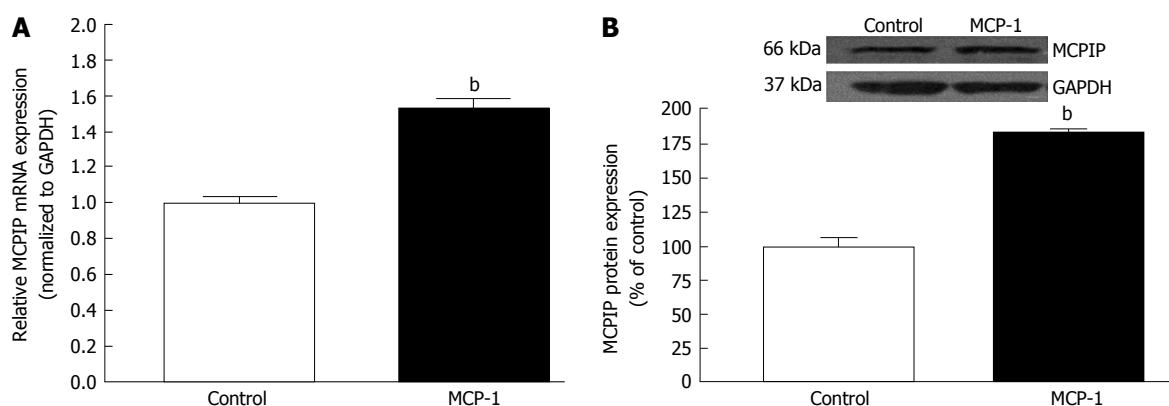


Figure 6 Monocyte chemoattractant protein up-regulates monocyte chemoattractant protein-1 induced protein expression in ARPE-19 cells^[140]. Monocyte chemoattractant protein-1 (MCP-1) increases MCP-1 induced protein (MCP-IP) mRNA (A) and MCP-IP protein expression (B) in human retinal pigment epithelium cells. The maintenance medium was deprived of phenol red for 2 d. Medium FBS content was then brought down from 10% to 1% for 1 d. Subsequently, cells were treated with 50 pg/mL MCP-1 for 24 h in a medium supplemented with 0.1% FBS. Cell homogenates were collected to assess MCP-IP expression by real-time PCR and Western blot. GAPDH was used as control. Data are mean \pm SE ($n = 4$). ^b $P < 0.01$ vs control cells; FBS: Medium with fetal bovine serum; PCR: Polymerase chain reaction; GAPDH: Glyceraldehyde 3-phosphate dehydrogenase.

of DR^[28]. An increase of angiotensinogen, ACE, ACE2, and AT1R in retinas from diabetic animals was described previously^[35,146,147]. Up to now, research addressed to find a link between the RAS and retinopathy has been based on the retinal microvasculature. Strong evidence supporting a role of Ang II in pericytes and endothelial cells in the retinal microvasculature has been shown. Ang II has a mitogenic effect on retinal endothelial cells^[23,59,148]. This peptide also decreases the expression of pigment epithelium derived growth factor^[148] and enhances proliferation of endothelial cells in retina through VEGF up-regulation^[23,149]. Moreover, glucose ingestion by the retinal tissue might be instantly regulated by Ang II^[150,151]. This increase in glucose in turn could induce VEGF expression and potentiates the effect of Ang II on VEGF expression as demonstrated previously in vascular smooth muscle cells^[152]. Since it is clear that reactive oxygen species (ROS) contribute to cellular damage in DR by inducing VEGF^[153,154], and that both Ang II and high glucose can lead to ROS formation,^[155,156] ROS may be a common pathway linking a synergistic effect between Ang II and high glucose on the activation of VEGF.

The actions of Ang II on the retinal vasculature have been well described in pericytes. These microvascular cells are incriminated in the regulation of capillary tone^[157], and it has been suggested they have other extra roles such as preservation of microvascular homeostasis^[149]. For instance, death of pericytes has been linked to the initial sign of DR. It has been reported that Ang II uncouples pericytes from the vasculature^[48,158]. Studies *in vitro* have shown activation of pericyte migration by Ang II through the AT1R^[159,160]. Moreover, Ang II also has an effect on pericyte viability, by increasing apoptosis^[33,59]. Therefore, it is evident that Ang II impacts the retinal microvasculature. Research in diabetic animals showed a reduction in the retinal microvascular injury by exposure to ACE inhibitors and AT1R blockers. These data revealed a decrease in the vascular leakage, acellular capillaries formation, VEGF production^[161-164], leukostasis and adhesion

molecules^[164-167]. Comparable advantages were observed in different animal models of diabetes, which were treated with renin inhibitors^[167], PRR inhibitor^[35], and gene delivery of ACE2^[160] respectively. Diabetes may also affect neuronal retina in DR. For example, diabetic retina may reveal releasing of pro-inflammatory factors by microglia^[168], death of retinal neurons^[169], apoptosis of ganglion cells^[170], glial dysfunction^[170] and photoreceptors loss^[171]. These pathological neuronal effects may be translated to electrophysiological abnormalities^[172-174]. Color vision, contrast sensitivity and dark adaption^[24,175] can be altered by diabetes before the presence of any apparent pathological sign in the vessels^[175]. Given that treatment with ACE inhibitors and AT1R blockers decreases these deficits in retinal function^[176-179], the advantages of RAS blockade could extend to non-vascular cells.

It is also interesting to note that discovery of other important players on the RAS such as ACE2 and Ang (1-7) has resulted in the emerging new role ascribed to these RAS components beyond the classic ACE/Ang II/AT1R axis of the RAS^[179-180]. Nevertheless, the force of this novel axis stays inadequately elucidated^[180,182-184]. This new protective axis antagonizes the classic role of the vasoconstrictor axis. Thus, it was assumed that a disproportion in the vasoprotective/vasodeleterious axis of the RAS, could result in the development and progression of DR. Many studies in non-ocular tissues have emphasized the beneficial effect of the balance displacement of the RAS towards the ACE2/Ang (1-7)^[180,185-189]. Therefore, activation of the vasoprotective axis is currently considered to be part of the beneficial actions of ACEi and ATRs blocker drugs^[180,182], which neutralize the actions of Ang II, in spite of its origins of generation^[146].

High blood pressure is a great risk factor for DR. Several studies have been addressed to elucidate if the contribution of the Ang II to the development of DR is *via* blood pressure dependent or independent. This is an intricate search, given that blockers of some compound of the RAS decrease both blood pressure and the actions

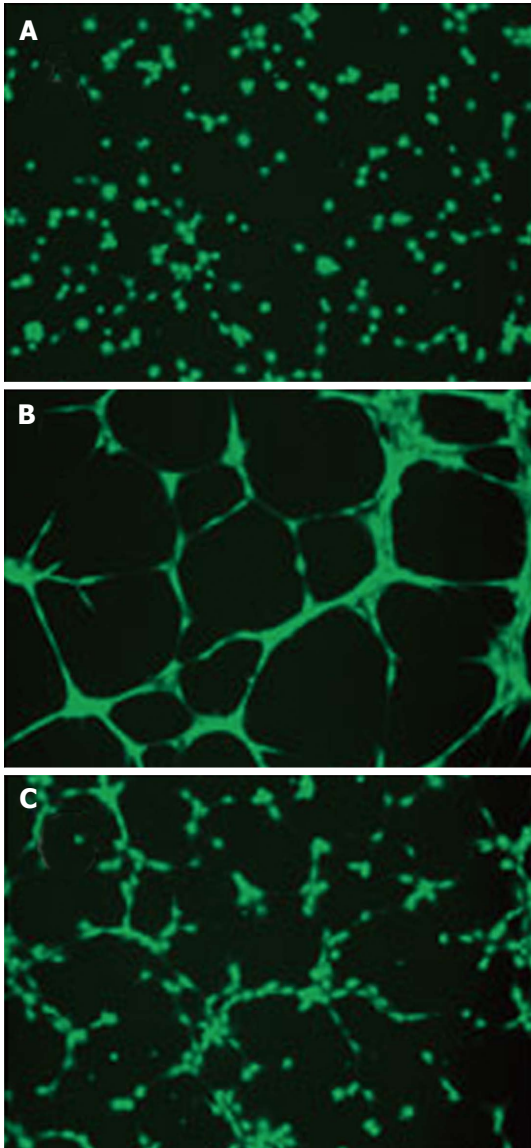


Figure 7 Conditioned medium collected from human ARPE-19 cells exposed to Ang II promotes tube formation in choroidal microvascular endothelial through AT1 activation^[140]. Cells were exposed to: (1) Ang II alone; or (2) Ang II in combination with candesartan for 24 h, supernatants were collected after treatment and human choroidal microvascular endothelial (cECs) were treated with the supernatants for 24 h. Thereafter, cells were trypsinized and then seeded (42000 cells/cm²) on a 24-well polystyrene plate coated with Geltrex™ (50 µL/cm²) according to the manufacturer's protocol followed by incubation in EBM medium for 24 h at 37 °C in 5% CO₂. At 16 h post-seeding, 2 µg/mL of Calcein, AM (Invitrogen, Cat # C3099), was added directly to the culture well and allowed to incubate for 20 min (37 °C, 5% CO₂). Cells were visualized using a fluorescence microscope. A: Control; B: cECs exposed to conditioned medium from Ang II-treated ARPE-19 cells; C: cECs treated with medium collected from treated retinal pigment epithelium cells. EBM: Endothelial cell basal; AM: Acetoxymethyl.

of the Ang II at cellular levels. Studies in Ren-2 rat with hypertension showed that both AT1R and β -adrenergic blockade regularize blood pressure^[158]. Nevertheless, the retinal vascular pathology only becomes better using AT1R blockers. Additional determination of the blood pressure-independent effects of the RAS blockade in DR is crucial for diabetic patients without hypertension.

The mechanism(s) by which the RAS exerts its effects in the retina are being investigated. There is proof that hypertension and mechanical stretch up-regulate the RAS and VEGF expression^[190]. It has been previously demonstrated an increase of VEGF in the RPE^[191] and in retinal endothelial cells^[192] due to mechanical stretch. Moreover, rats with hypertension showed increased expression of the VEGFR-2 in the retina^[191]. Therefore, it could be probable that the decrease in VEGF reported in DR^[193] following RAS blockade could be due to the antihypertensive properties of this treatment, rather than, suppression of the growth factor effects of Ang II. Moreover, given that a relationship between ROS and cellular damage in DR has been demonstrated and the fact that ROS production is induced by Ang II^[153,154,194,195], it is likely that ROS are essential in the pathogenesis of DR. The main origin of the ROS is nicotinamide adenine dinucleotide phosphate (NADPH, or NOX) and ROS originated from NOX have been associated with the development of DR^[196,197]. Ang II modulates NOX to generate ROS^[194,198]. However, the connection between the RAS and NOX in retinopathy is not completely clarified yet^[199,200]. Obviously, the link involving RAS and NOX in DR guarantees further study.

Clinical trials evaluated the influence of Ang II in the development and progression of DR. To elucidate this, three major studies addressed to evaluate the blockade of the RAS were done: (1) the DIabetic RETinopathy Candesartan trial^[201-204]; (2) the Appropriate Blood Pressure Control in Diabetes trial^[205]; and (3) the Action in Diabetes and Vascular Disease Controlled Evaluation (ADVANCE) trial^[206]. The first study showed that candesartan, an AT1R blocker, modestly avoid the evolution of retinopathy in type 1 diabetic patients without hypertension. From another point of view, this AT1R blocker caused reversion of retinopathy in type 2 diabetic patients in a 34% regression of retinopathy and decreased the risk of microaneurysm evolution in both types of diabetes^[202]. The second trial study, showed notably benefit for RAS blockade^[203], whereas the ADVANCE study reported that treatment with a combination of an ACE inhibitor and a diuretic, did not affect the retinopathy risk^[205]. I summary, these data document the influence of Ang II in the development of DR. Further evaluation of the RAS blockade in DR is still to be determined.

CONCLUSION

Hypertension is a potential link between cardiovascular pathologies and eye diseases. A large amount of information has demonstrated the presence of a RAS in the retina which is greatly spread in the vasculature. To date, findings from epidemiological studies indicate an association between AMD and hypertension. Moreover, studies *in vitro* and *in vivo* show that Ang II contributes to sub-RPE deposit formation and CNV development and that these events can be improved by Ang II receptor blockers (ARBs). However, the utility of ARBs for the treat-

ment of eye AMD is still to be determined. In terms of DR, there is documented evidence showing a clear contribution of Ang II to the development of this disease. Therefore, the use of ARBs can confer retinoprotection and arrest the progression of DR.

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Is ABO blood group truly a risk factor for thrombosis and adverse outcomes?

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Abstract

ABO blood type is one of the most readily available laboratory test, and serves as a vital determinant in blood transfusion and organ transplantation. The ABO antigens are expressed not only on red blood cell membranes, determining the compatibility of transfusion, but also on the surface of other human cells, including epithelium, platelet and vascular endothelium, therefore extending the research into other involvements of cardiovascular disease and postoperative outcomes. ABO blood group has been recognized as a risk factor of venous thrombosis embolism since the 1960's, effects now understood to be related to ABO dependent variations are procoagulant factor VIII (FVIII) and von Willebrand factor (vWF) levels. Levels of vWF, mostly genetically determined, are strongly associated with venous thromboembolism (VTE). It mediates platelet adhesion aggregation and stabilizes FVIII in plasma. Moreover, many studies have tried to identify the relationship between ABO blood types and ischemic heart disease. Unlike the clear and convincing associations between VTE and ABO blood type, the link between ABO blood type and ischemic heart disease is less

consistent and may be confusing. Other than genetic factors, ischemic heart disease is strongly related to diet, race, lipid metabolism and economic status. In this review, we'll summarize the data relating race and genetics, including ABO blood type, to VTE, ischemic heart disease and postoperative bleeding after cardiac surgery.

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Key words: ABO blood group; Venous thrombosis; Ischemia disease; Cardiac surgery; Outcomes

Core tip: In this review, we updated the reports regarding the associations between ABO blood groups and venous thrombosis, ischemic heart disease as well as postoperative outcomes after cardiac surgery. ABO blood group is clearly associated with venous thromboembolism whereas critical review of the literature reveals a more controversial relationship with atherosclerosis, arterial thrombosis and postoperative outcomes.

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INTRODUCTION

The ABO group of human red cell antigens was discovered by Karl Landsteiner in 1900. ABO antigens are carbohydrate molecules that are the major determinants of the compatibility of red cell transfusions. Naturally occurring, complement fixing IgM antibodies are formed against the A and B antigens in individuals that do not express them on their red cell surfaces and therefore recognize them as foreign antigens. Each individual inherits

Table 1 The incidence of ABO phenotypes in populations from different racial backgrounds

Race	Blood group phenotype O ¹ (O ² rare)	Blood group genotypes				
		A ¹	A ²	B	A ¹ B	A ² B
Caucasian	44%	33%	10%	9%	3%	1%
Asian	43%	27%	Rare	25%	5%	Rare
African	49%	19%	8%	20%	3%	1%

Illustrations: Sub-group A2 expresses less A antigen on the red cell surface and has been referred to as “weak” A.

Table 2 The association of ABO genotype with von Willebrand factor and factor VIII levels is presented with categorization by von Willebrand factor levels

	Genotype	Median value	
		vWF	FVIII
Low	O ¹ O ¹	69%	75%
Medium	A ¹ O, A ² O, BO	89%	96%
High	AA, BB, A ¹ B	120%	117%
Highest	A ² B	169%	112%

vWF: Von Willebrand factor; FVIII: Factor VIII.

two ABO alleles. The A and B alleles encode separate glycosyltransferase that add N-acetylgalactosamine and D-galactose of the “H” antigen (group O determinant), converting it into A and B antigens respectively. However, as the O allele does not express either A or B transferase enzymes, continued expression of the unaltered H antigen is the phenotypic marker of the O blood group^[1]. The ABO antigens are expressed not only on red blood cell membranes, determining the compatibility of transfusion, but also on the surface of other human cells, including epithelium, platelet and vascular endothelium^[2], therefore extending potential pathophysiology into other areas of cardiovascular disease and postoperative outcomes.

Expression of the different ABO phenotypes is partially dependent on racial origin as shown in Table 1, with Group O generally being the most common blood group^[3]. Blood groups are basically described by phenotypes, because historically blood groups are determined by commercial antibodies that recognize A and B antigens. By this detection method, both AO and AA genotypes (A¹O¹, A¹A²) will be identified as group A, while BO and BB genotypes as group B. In this review, we updated the reports regarding the associations between ABO blood groups and venous thrombosis, ischemic heart disease as well as postoperative outcomes in terms of both ABO phenotype and genotype.

ABO AND VON WILLEBRAND FACTOR

Von Willebrand factor (vWF) has two major biological forms and the high molecular weight vWF (HMW vWF) is hemostatically more active than the low molecular weight vWF (LMW vWF)^[4]. HMW vWF mediates the interaction between platelets and damaged areas of the blood vessel wall, while LMW vWF acts as a specific car-

rier molecule for procoagulant factor VIII (FVIII), thereby localizing FVIII to the site of any vascular injury. Both are essential for normal hemostasis^[5,6].

Plasma vWF levels are generally reported to be approximately 25% higher in non-O blood individuals^[7]. Synthesized in endothelial cells and megakaryocytes, the HMW vWF, enters the plasma from platelet granules following platelet activation and degranulation at the site of tissue injury, or alternatively being stored in endothelial cell Weibel-Palade bodies, then secreted in response to thrombin, fibrin or histamine stimulation^[8]. vWF molecular has three binding sites, platelet glycoprotein 1b binds to A1 domain, while collagen binds to A3 domain, forming the primary hemostatic clot^[9,10]. The A2 domain binds to ADAMTS13 and is responsible for vWF cleavage (Figure 1).

Clinical observations that the severity of bleeding in mild von Willebrand's disease was exaggerated for group O patients led to the recognition of an ABO dependent variation in vWF levels^[11-13]. A formal linkage analysis showed the effect of ABO blood type on von Willebrand factor is a direct functional effect of the ABO locus, rather than linkage disequilibrium between the ABO locus and another unidentified VWF regulation locus^[14]. vWF levels can also influence procoagulant FVIII levels since vWF is a carrier molecule that protects FVIII from proteolysis in plasma.

Moeller *et al.*^[15] compared vWF and FVIII levels in individuals of different ABO phenotype and found ascending order O < A < B < AB for vWF level and O < A < AB < B for FVIII level. This effect becomes more nuanced when considering the specific genotypes that result in ABO phenotypes, as illustrated in Table 2. Within A and B phenotypes, vWF concentrations in AA or BB are slightly higher than AO or BO^[16] and A¹ and B alleles are found to be associated with higher vWF and FVIII levels, while A² is comparable to O allele^[6,11,13,17].

MECHANISM FOR ABO RELATED VARIABILITY IN VWF LEVELS

There is no direct evidence demonstrating that the ABO locus is associated with vWF synthesis^[8], therefore efforts to elucidate the association between ABO and vWF have focused on vWF metabolism and cleavage. ADAMTS13 cleavages HMW vWF to LMW vWF^[8,15,18,19], thereby modulating the tendency of vWF to cause platelet aggregation and thrombus formulation^[20]. The biological importance of this is exemplified by thrombotic thrombocytopenic purpura (TTP). In TTP, autoantibodies neutralize ADAMTS13 leading to diffuse microvascular thrombosis from the unregulated action of HMW vWF. This extreme example leads to a proposed mechanism for the ABO group related modulation of vWF levels and therefore tendency to thrombosis. While A, B and H antigens are more commonly known to be expressed on the cell surfaces of erythrocytes and various exocrine cells, they are also expressed on the vWF molecule. The

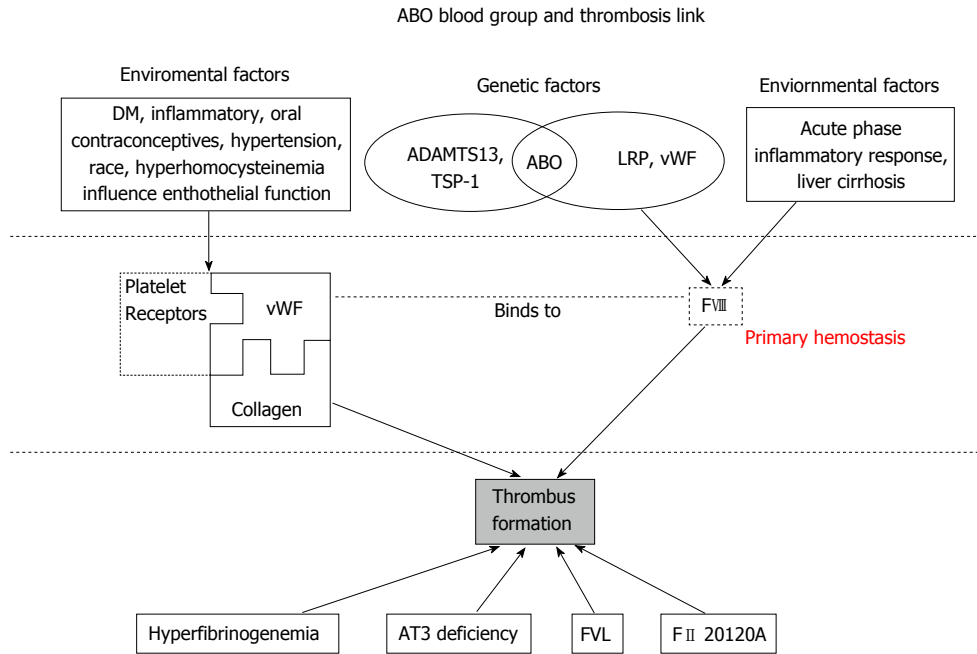


Figure 1 Genetic and environmental factors that contribute to increased levels of von Willebrand factor and factor VIII and risk of thrombus formation. AD-AMTS13: A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; AT3: Antithrombin III; DM: Diabetes mellitus; F II: Prothrombin gene mutation 20120A; FVIII: Factor VIII; FVL: Factor V leiden; LRP: Lipoprotein receptor-related protein; TSP-1: Thrombospondin-1; vWF: Von Willebrand factor.

location of the A, B and H antigens on the vWF molecule is thought to be close to the A2 domain binding site for ADAMTS13 and that A and B antigens reduce ADAMTS13 binding and, therefore, cleavage^[8,21]. Some studies confirmed this hypothesis by providing evidence that the proteolytic effect of ADAMTS13 on vWF was significantly faster in O group (only H antigen expression) than in non-O groups with A and B antigen expression^[22,23]. Factors other than ABO group can also modify vWF metabolism which may limit the direct association of ABO group with vWF levels and thrombosis, explaining some inconsistencies in the various studies we report. For example, thrombospondin-1 (TSP-1) has been reported to control vWF multimer size by both directly cleavage and indirectly, competing with ADAMTS13^[24,25]. Thus, any genetic factors influence cleavage (ABO blood type, ADAMTS13 and TSP-1) and environmental risk factors that affect endothelial cell function, such as age, diabetes mellitus, hypertension, inflammatory and oral contraceptive drugs, all contribute to the complex risk factors leading to clinical thrombosis. This concept is illustrated in Figure 1.

The link between ABO blood group, H antigen expression and lower vWF levels has been well established above. How this translates into a clinically relevant risk of thromboembolism manifesting either as venous thromboembolism or coronary artery thrombosis is discussed in detail below.

VENOUS THROMBOEMBOLISM

Venous thromboembolism (VTE) includes deep vein thrombosis and pulmonary embolism and is a serious

medical condition with a historical mortality rate of 10% and 15% respectively^[26]. ABO blood group has been recognized as a risk factor since the 1960's, effects now understood to be related to ABO dependent variations are procoagulant FVIII and vWF levels. Levels of vWF, mostly genetically determined, are strongly associated with VTE. It mediates platelet adhesion aggregation and stabilizes F VIII in plasma. In a healthy state, twin studies showed 75% of variance in plasma vWF levels result from genetic determinants^[27], 30% of which are associated with ABO blood type^[28]. Other non-genetic factors, such as aging, diabetes, free radical formation and inflammation, may have a more important role during acute illnesses or during the perioperative period^[29]. As shown in Figure 1, environmental causes of endothelial dysfunction can greatly affect vWF levels.

Numerous studies have reported that individuals with non-O blood types had a higher risk of VTE compared to their O counterparts^[30-34]. According to Wiggins, compared to O¹O¹ group, AB diplotype category has the highest VTE rate, followed by B allele and A¹ allele^[13]. Other rare genotypes like A³, A^x, A^a, B³, B^a were less amenable to statistically meaningful comparison in this study. These observations were supported by genotype association studies that showed H-antigen rich genotypes (O¹O¹, O¹O², O¹A²) have a lower incidence of VTE than H-antigen poor genotypes (A¹B, O¹A¹, O¹B)^[17,35,36], establishing ABO blood type as an important risk factor for VTE^[37].

In Figure 1, various genetic and environmental factors affecting vWF levels are presented. What's more, FVIII, circulating bound to vWF, also plays a crucial and independent role in the propagation phase of coagulation

Table 3 Outline of the main studies describing the association of ABO blood type and manifestations of atherosclerotic heart disease

Ref.	Population	Sample size	Outcome(s)	Findings
Garrison <i>et al</i> ^[44]	United States		"Cardiovascular disease"	O showed the lowest incidence
Whincup <i>et al</i> ^[45]	United Kingdom (men only)	7662	CAD	Individuals with A blood type has higher incidence of CAD (RR = 1.21, CI: 1.01-1.46)
Rosenberg <i>et al</i> ^[46]	United States (young women)	225 MI vs 802 controls	MI	Blood group A was associated with MI
Lee <i>et al</i> ^[47]	Taiwan (young patients)	136 CAD vs 129 without CAD	CAD and MI	Group A was associated with increased risk of CAD (OR = 2.61, CI: 1.11-6.14) and MI (OR = 3.53, CI: 1.21-10.29)
Sari <i>et al</i> ^[48]	Turkish	476 MI vs 203 healthy control	MI	ABO blood type is not associated with development of MI
Carpeggiani <i>et al</i> ^[49]	Italy	4901	MI and CAD	Group non-O is associated with increased mortality in patients with CAD, groups A and B prevail in MI
Nydegger <i>et al</i> ^[50]		177 patients vs 89 control	MI	B allele carriers had higher MI (OR = 2.7, CI: 1.1-6.8)
Stakisaitis <i>et al</i> ^[51]	Lithuania	441	CAD	B blood group can be related with CAD in women
Meade <i>et al</i> ^[52]	United Kingdom	1393 men with 178 IHDs	CAD and MI	Incidence was significantly higher in blood group AB
Mitchell <i>et al</i> ^[53]	United Kingdom		"Cardiovascular disease"	Towns with higher prevalence of group O have higher rate of cardiovascular mortality
Biswas <i>et al</i> ^[54]	India	250 CAD vs 250 controls	CAD	Group O increases the risk of CAD
Amirzadegan <i>et al</i> ^[55]	Iran	2016 patients	CAD	No correlation
Biancari <i>et al</i> ^[56]	Finland	1152 CABG patients	MI	No correlation
He <i>et al</i> ^[57]	United States	89501	Coronary heart disease	AB group has highest CAD risk, followed by groups B, A and O

CAD: Coronary artery disease; MI: Myocardial infarction.

activation^[6]. Since vWF is the plasma co-carrier of FVIII, ABO blood type, by altering vWF levels, also exerts an effect on FVIII levels. Tirado *et al*^[34] demonstrated that genetic factors explain 40% of the variance of FVIII levels; other studies further identified a quantitative trait locus and the ABO locus as two major genetic factors underlining the variability of FVIII levels^[14,38]. Unconnected to ABO group, lipoprotein receptor-related protein has also been identified to be associated with degradation of FVIII, another consideration when evaluating variance in FVIII levels^[39]. In summary, while ABO blood type and vWF levels are two important factors commonly known to modulate FVIII plasma level, the biology determining FVIII is a complex interaction of genetic and environmental factors as illustrated in Figure 1.

However, FVIII may have some effect independent of vWF. Some studies demonstrated that a high FVIII level is persistent beyond the acute phase state^[40,41], representing a potential risk factor for delayed or recurrent thrombosis. In addition, Morange *et al*^[17] described a residual statistical effect of ABO blood group on FVIII levels after adjustment for vWF levels, postulating that FVIII is an independent VTE risk factor^[29,34]. Additionally, FVIII was reported to be associated with recurrent disease^[34], consistent with reports that non-O carriers had a higher incidence of VTE recurrence than O carriers^[42,43].

ISCHEMIC HEART DISEASE

Unlike the clear and convincing associations between VTE and ABO blood type, the link between ABO blood type and ischemic heart disease is less consistent and may be confusing. In part this can be due to the inclusion of different end-points that may represent different disease

processes, such as angina/atherosclerosis (less likely ABO/vWF related) or myocardial infarction (MI)/coronary thrombosis (more likely ABO/vWF related). The pathogenesis of coronary artery disease (CAD) involves the progression of an atherosclerotic disease process, whereas MI (or acute coronary syndrome) results from a platelet rich thrombus forming on abnormal endothelium diseased by the atherosclerotic process. Platelet rich thrombi (MI) are reliant on primary hemostasis, whereas the mechanism linking ABO group to CAD is less obvious. However, it is important to evaluate ABO group as a risk factor for both these devastating conditions: CAD and MI.

Many studies show that non-O group have higher incidence of ischemic heart disease (Table 3). The Framingham Heart study, and others, suggested A blood type has increased risk of CAD^[44-46] and MI^[47]; more specifically, A blood group seems to be related to early CAD detection^[47,48] and predominates in patients with MI^[49]. Other studies noted groups B^[50,51] or AB^[52] have higher incidence of CAD. Conversely, Mitchell^[53] reported that towns with a higher prevalence of group O have higher rates of cardiovascular mortality and an Indian study with moderate sample size also showed O blood group is more frequent in CAD and increased the risk of CAD^[54]. Further studies do not identify any association between blood type and CAD^[55,56]. Based on these inconsistent results and relative small sample sizes. He^[57] conducted a meta-analysis of two large, prospective studies consisting of 89501 participants, and found the highest risk of CAD was observed in blood group AB, followed by group B, A and O. This is consistent with what we know about ABO related vWF/FVIII levels with the highest in group AB, followed by group B, A and O. According to

this meta-analysis, non-O group has an 11% increased risk of CAD, an association not altered by adjusting for other co-morbidities. There was, however, no difference in survival and, paradoxically, a trend towards increased mortality and/or non-fatal myocardial infarction in O blood type patients.

The relationship between ABO genotype and CAD has also been investigated. Wiggins *et al.*^[13] reported an 18% increased MI risk associated with A¹¹ allele carriers compared to O¹O¹ homozygotes, but no other associations were found between B or AB alleles and MI, possibly due to underpowering as B and AB groups are relatively rare. An investigation of postmenopausal women suggested A or B allele carriers almost had two-fold incidence of acute ischemic heart disease compared to OO^[58]. Similarly, Nydegger *et al.*^[50] showed a three-fold risk of MI with the presence of B allele (genotype AB, BB or BO) compared to non B allele (genotype OO, AO, AA) in a smaller case-control study. Another study^[59] with angiography showed O¹ allele carriers had a 39% decreased risk of MI compared to non O¹. More obviously, von Beckerath *et al.*^[59] found a dose-dependent effect with carriage of one or two O¹ alleles being associated with decreased risks of acute MI. However, a recently published study by Reilly *et al.*^[60] argued that ABO locus did not predict MI in patients with known CAD, but was strongly associated with the presence of CAD in two large genome wide association studies. Whether ABO alleles are associated with the development of MI or only the presence of CAD is not yet clearly defined. It is much easier to investigate the risk factors for CAD prevalence in a cross-sectional study than to evaluate the incidence of MI with a prospective design, as the latter requires a stable cohort with years of detailed follow-up. Currently, the association of MI and ABO blood group has only been well reported in survivors of MI events. This introduces bias, as patients may suffer an asymptomatic MI, not present at hospital, or die before diagnosis.

There are some mechanisms proposed to explain the association between ABO blood type and CAD, but a unifying theory remains elusive. Along with fibrinogen, vWF may play a role in the progression of atherosclerosis by promoting platelet aggregation and adhesion^[21]. On the other hand, blood group A has been noted to have higher levels of cholesterol and low density lipoprotein^[61], which may partly explain the association with an increased risk of CAD. Additionally, the ABO locus was recently reported to be associated with CAD related inflammatory makers, including intercellular adhesion molecule-1, soluble P-selectin^[62], soluble E selectin^[63] and tumor necrosis factor- α ^[53]. Still, the interactions among genetic factors (known genes increasing susceptibility to CAD and the ABO locus) and environmental factors conferring risk for CAD and MI are complicated. It is unclear which ABO phenotypes or genotypes increase CAD and/or MI risk; this risk may differ for the incidence of CAD or MI and survival following MI.

CARDIAC SURGERY

Our group performed a retrospective study to evaluate the relationship between ABO blood types and postoperative bleeding in cardiac surgical patients. This was based on the hypothesis that lower circulating vWF levels seen with group O may reduce primary hemostasis resulting in increased postoperative bleeding. While group O did have impaired baseline measures of primary hemostasis and required less heparin and protamine for perioperative anticoagulation, the result showed no difference of postoperative bleeding between different blood groups^[20]. Limitations of such perioperative studies are the lack of intermediate, mechanistic measures of factor levels and the confounding effects of the acute phase response that may drown out an ABO effect. Also, the classification by phenotype is limited. For example, the A²O genotype with low vWF levels and the A¹A¹ genotype with high vWF levels are both classified as group A. In addition, the statistically convenient categorization into O and non-O phenotype is flawed for the same reason, blurring comparison between H antigen rich and H antigen poor genotypes that have been shown to drive the association between ABO blood type and outcome. As an alternative approach, we have preliminary results suggesting that the AB phenotype (no H antigen) requires less perioperative transfusion than non-AB phenotypes and this is associated with better postoperative survival for the rare AB group. These findings require confirmation with prospective study.

CONCLUSION

In summary, ABO blood group is an important determinant of vWF and FVIII levels which in turn confer a clear risk of increased VTE with the higher levels seen in the non-O blood types. The associations are far less clear for CAD and MI but a similar pattern emerges with most studies finding group O to be at lower risk. In terms of perioperative bleeding and transfusion, a possible reciprocal for thrombosis, further work needs to be done to determine a consistent ABO effect.

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Cardiac manifestations in systemic sclerosis

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Abstract

Primary cardiac involvement, which develops as a direct consequence of systemic sclerosis (SSc), may manifest as myocardial damage, fibrosis of the conduction system, pericardial and, less frequently, as valvular disease. In addition, cardiac complications in SSc may develop as a secondary phenomenon due to pulmonary arterial hypertension and kidney pathology. The prevalence of primary cardiac involvement in SSc is variable and difficult to determine because of the diversity of cardiac manifestations, the presence of subclinical periods, the type of diagnostic tools applied, and the diversity of patient populations. When clinically manifested, cardiac involvement is thought to be an important prognostic factor. Profound microvascular disease is a pathognomonic feature of SSc, as both vasospasm and structural alterations are present. Such alterations are thought to predict macrovascular atherosclerosis over time. There are contradictory reports regarding the prevalence of atherosclerosis in SSc. According to some authors, the prevalence of atherosclerosis of the large epicardial coronary arteries is similar to that of the general population, in contrast with other rheumatic diseases such as rheumatoid arthritis and systemic lupus erythematosus. However, the level of inflammation in SSc is inferior. Thus, the atherosclerotic process may not be as aggressive and not easily detectable in smaller studies. Echocardiography (especially tissue

Doppler imaging), single-photon emission computed tomography, magnetic resonance imaging and cardiac computed tomography are sensitive techniques for earlier detection of both structural and functional scleroderma-related cardiac pathologies. Screening for subclinical cardiac involvement *via* modern, sensitive tools provides an opportunity for early diagnosis and treatment, which is of crucial importance for a positive outcome.

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Key words: Systemic sclerosis; Cardiac involvement

Core tip: The prevalence of primary cardiac involvement in systemic sclerosis (SSc) is difficult to determine, as it can manifest as myocardial damage, fibrosis of the conduction system, pericardial and valvular disease. When clinically manifested, cardiac involvement is thought to be an important prognostic factor. Echocardiography, magnetic resonance imaging and computed tomography are sensitive techniques for earlier detection of structural and functional SSc-related cardiac pathologies. Screening for subclinical cardiac involvement provides an opportunity for early diagnosis and treatment, which is of crucial importance for a positive outcome.

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INTRODUCTION

Systemic sclerosis (SSc) is a chronic multisystem disease characterized by microangiopathy, fibrosis of the skin and internal organs, and autoimmune disturbances. Two major subsets are recognized, namely, SSc with limited cutaneous involvement (skin thickening is localized to the face, neck and extremities distal to elbows and knees) and

SSc with diffuse cutaneous involvement (skin thickening also involves the extremities proximal to elbows and knees, chest, abdomen and back).

Primary cardiac involvement, which develops as a direct consequence of SSc, may manifest as myocardial involvement, fibrosis of the conduction system, pericardial and, less frequently, as valvular disease. Furthermore, cardiac complications in SSc may develop as a secondary phenomenon due to pulmonary arterial hypertension (PAH), interstitial lung disease, and kidney pathology^[1,2].

PRIMARY CARDIAC INVOLVEMENT IN SSc

The prevalence of the primary cardiac involvement in SSc is difficult to determine due to the numerous possible cardiac manifestations, the applied diagnostic tools and diverse patient populations. Of note, the results of histologic studies, which frequently reveal the presence of myocardial involvement, often disagree with those of the clinical studies, performed with different assessment techniques^[3].

Clinical examination and routine non-invasive investigations, such as electrocardiogram and thoracic X-ray, are applied in the everyday cardiac assessment, but their sensitivity is low^[1,4,5]. Echocardiography [especially tissue Doppler imaging (TDI)], cardiac computed tomography (CT), single-photon emission CT (SPECT), magnetic resonance imaging (MRI), positron emission tomography (PET), and radionuclide ventriculography are sensitive techniques for earlier detection of both structural and functional scleroderma-related cardiac pathologies^[1]. In the recent years, with the improvement of the prognosis of scleroderma renal crisis (SRC), pulmonary and cardiac involvement are the main causes for disease-associated mortality in SSc. Signs for cardiac involvement have been detected with a prevalence of 15% in a cohort of 953 patients with diffuse cutaneous SSc based on clinical findings, echocardiography, electrocardiography, or Holter monitoring^[6]. Asymptomatic decreases in the ejection fraction, asymptomatic pericardial effusion, or asymptomatic arrhythmias were not considered as significant heart manifestations in this study. Disease-associated mortality was found to be 20% in a ten-year follow-up^[5,6]. The greatest impact occurred in the first five years (14% mortality rate).

Conventional echocardiography is used for cardiac assessment in most studies. Depressed left ventricle (LV) contractility has been reported in only a few patients, whereas up to 40% present with relaxation abnormalities, valvular regurgitation and possible right ventricular (RV) pathology^[3]. A recent analysis of organ involvement in a large cohort of 9165 SSc patients from the European League Against Rheumatism Scleroderma Trials and Research database revealed that diastolic dysfunction was among the most frequent features (17.4%). Palpitations were also a common finding in 23.7% of the cases, whereas conduction blocks were detected in 11% by

electrocardiography^[7]. In a cohort of 1012 Italian SSc patients, the prevalence of cardiac symptoms of arrhythmia was 35%^[3].

LV systolic dysfunction is among the rarest findings in SSc patients. In a large multi-centered study, which included 570 SSc patients, the prevalence of LV systolic dysfunction was found to be 1.4%, whereas LV hypertrophy and LV diastolic dysfunction were observed in 22.6% and 17.7% of patients, respectively^[8]. In a recent, large European League Against Rheumatism Scleroderma Trials and Research study (including 7073 consecutive SSc patients with a mean age of 56 ± 14 years) the prevalence of reduced LV ejection fraction was found to be 5.4%^[9].

Of note, cardiac MRI detected heart pathologies in up to 75% (39/52) of cases, including increased intensity signal of the myocardium in T2, thinning of the LV, pericardial effusion, reduced LV and RV ejection fractions, LV diastolic dysfunction and kinetic abnormalities, and myocardial delayed contrast enhancement^[10]. Echocardiographic signs of heart abnormalities were also observed in 48% (25/52) of these patients, which underlines the superior sensitivity of the cardiac MRI modality. Cardiac MRI can be used to diagnose both structural and functional pathologies, such as myocardial inflammation and fibrosis (the extent of fibrosis and viable tissue is properly measured after contrast enhancement). The method gives an opportunity for quantitative assessment of myocardial perfusion and the effect of vasodilators^[3,10].

TDI also demonstrates an increased proportion of LV abnormalities in SSc patients. In 101 SSc patients, conventional echocardiography detected low LV ejection fraction (< 55%) in 7% (7/100) of patients, which was doubled to 14% (14/100) by use of TDI^[11-14].

Appearance of exercise-related changes should also be taken into account. Thus, using radionuclide ventriculography in 19 SSc patients, a reduced LV ejection fraction has been detected in 10.5% (2/19) of patients at rest, while the values were abnormal in 36.8% (7/19) after exercise^[15].

Thallium scintigraphy is another sensitive technique that detects perfusion defects in more than 70% of SSc patients with and without clinically manifested myocardial involvement^[16].

Some studies have found that scleroderma-related cardiac manifestations occur in both diffuse and limited cutaneous forms of SSc, whereas according to others, the prevalence is greater in the diffuse cutaneous form of the disease. An association between the cardiac involvement and the presence of anti-topoisomerase, anti-U3RNP antibodies, rapidly evolving skin disease, and skeletal myopathy has been implicated^[1,17,18].

When clinically manifested, cardiac involvement is thought to be an important prognosis factor^[3,19].

Myocardial involvement

The general pathogenetic mechanisms in SSc, including microvascular alterations (vasospastic episodes that are functional in the beginning with subsequent morphological vascular damage), collagen accumulation by activated

Table 1 Features of myocardial involvement in systemic sclerosis distinct from coronary atherosclerotic disease

Characteristic features
Microvascular ischemia
Patchy fibrosis, unrelated to coronary epicardial artery distribution
Involvement of immediate subendocardium, which is spared in atherosclerosis
Contraction band necrosis
Concentric intimal hypertrophy associated with fibrinoid necrosis of intramural coronary arteries
Hemosiderin deposits are not typically seen; they are evident in the atherosclerotic process

fibroblasts, and complex immune disturbances, are also thought to be involved in the pathogenesis of myocardial heart involvement in SSc^[3,20]. The ischemic, fibrotic and inflammatory lesions, which develop as a result of the above-mentioned processes, may also affect the conduction system, the pericardium, and the endocardium.

The consequences of the pathogenetic processes in SSc at the myocardial level result in areas of focal ischemia, recurrent ischemia-reperfusion injury, myocarditis and myocardial fibrosis. Microvascular alterations, but not the traditional atherosclerotic coronary disease, are thought to play a major role in the development of myocardial blood flow disturbances in SSc. Of note, myocardial infarction has been described in SSc patients with unaltered coronary arteries. Vasospasm of the small coronary arteries and arterioles (the so-called myocardial Raynaud's phenomenon) is considered to be involved in the early scleroderma-related ischemic myocardial changes with subsequent ischemia reperfusion injury and the development of structural vascular alterations. The early functional and reversible abnormalities have been demonstrated with thallium-201 SPECT at rest, after exercise and cold stimulation, PET, and cardiac MRI. In addition, an impaired vasodilator reserve has been found in SSc after causing maximum vasodilation with intravenous dipyridamol^[1,21].

A "mosaic", "patchy" distribution of myocardial fibrosis is a pathognomonic feature of the disease. In addition, foci of contraction band necrosis are typically found in all parts of the myocardium, including the immediate subendocardial area, which is usually spared in atherosclerotic processes^[22,23] (Table 1). At histological examination, distinct differences between myocardial fibrosis due to SSc itself and fibrosis in the context of coronary artery disease have been noted^[20]. In scleroderma-related heart involvement, the fibrotic areas do not correlate with pathologic changes of a single coronary artery. Hemosiderin myocardial deposits that are typically seen in atherosclerosis are absent in SSc-related myocardial pathology.

The inflammatory and autoimmune nature of SSc, as well as its possible association with skeletal myopathy, suggests that myocardial inflammation may play a crucial role in SSc heart disease. Myocarditis has been occasionally reported in SSc patients with acute and severe

cardiac symptoms^[21,24]. Interestingly, in a cohort of 181 SSc patients, a recent-onset heart disease was registered in 7 patients who underwent extensive noninvasive and invasive evaluations, including MRI and endomyocardial biopsy^[21]. Strikingly, all SSc patients with newly developed symptoms and signs of cardiac involvement were found to have biopsy-proven myocarditis. Administration of immunosuppressors (corticosteroids, cyclophosphamide, azathioprine) led to significant clinical improvement, normalization of cardiac enzymes, and improvement of MRI findings in nearly all cases.

Of note, a slightly increased thickness of the septum and posterior wall, or asymmetric septal hypertrophy have been found in a significantly higher number of SSc patients, including those without systemic arterial hypertension, as compared with healthy controls. Septal hypertrophy has also been observed secondary to PAH, which is often subclinical^[1].

The main clinical consequence of myocardial lesions is diastolic LV dysfunction, and less frequently systolic dysfunction, which both may be asymptomatic. In addition, different forms of atrial and ventricular arrhythmias, as well as symptomatic heart failure, may occur^[1,20].

Treatment

The administration of vasodilators, such as calcium channel blockers and angiotensin converting enzyme (ACE) inhibitors, has demonstrated beneficial effects on myocardial perfusion and limiting further progression of life-threatening complications^[5]. Improved myocardial perfusion and function in SSc patients with microvascular coronary pathology has been observed after treatment with nifedipine, nicardipine, or bosentan, using sensitive tests for evaluation such as cardiac MRI, TDI, and radionuclide ventriculography^[1,25-27]. Improved myocardial perfusion in scleroderma myocardial disease has also been found after treatment with ACE inhibitors^[28]. It has been hypothesized that there is a concomitant presence of ischaemic lesions accessible to reperfusion after vasospasm of small coronary vessels and irreversible lesions, such as morphological vessel pathology or myocardial fibrosis^[1]. Thus, administration of vasodilators may influence the reversible component of myocardial ischaemia.

A significantly lower number of SSc patients with reduced LV ejection fraction were found to have been previously treated with calcium channel blockers^[9]. These observations suggest that calcium channel blockers may protect against microvascular complications. Currently, dihydropyridine calcium channel blockers are the most well-studied and validated option for clinically apparent myocardial disease in SSc, and may be considered also for protective therapy. They have minimal negative inotropic effects and are generally well-tolerated, with reflex tachycardia and lower extremity edema being the most frequent side effects. Thus, they are recommended for regular administration in SSc-related myocardial disease unless contraindicated. In cases with concomitant PAH, they should be used with caution as they may lead to se-

vere systemic hypotension^[1].

Atherosclerosis

Accelerated atherosclerosis with increased cardiovascular morbidity and mortality is a well-known complication of many systemic inflammatory diseases that cannot be explained by the traditional cardiovascular risk factors. The hyperactivation of the immune system and systemic inflammation lead to premature atherosclerosis and earlier occurrence of its clinical manifestations. Thus, ischemic heart disease secondary to coronary atherosclerosis is the first cause of cardiovascular mortality in rheumatoid arthritis patients. Late mortality in systemic lupus erythematosus patients is mainly related to atherosclerotic disease, while in early phases, intercurrent infections are the leading cause^[29].

There are contradictory reports regarding the prevalence of atherosclerosis in SSc^[30]. According to some authors the prevalence of atherosclerosis of the large epicardial coronary arteries is similar to that of general population^[31]. In an autopsy study comparing 58 SSc cases to 58 controls, a significantly higher prevalence of ischaemic heart disease was found in the SSc patients^[32]. The frequency of epicardial vessel coronary atherosclerosis was similar (48% *vs* 43%), but atherosclerotic lesions of the small coronary arteries or arterioles occurred in 17% of SSc patients, compared with only 2% of controls. A study by Khurma *et al*^[33] comprised of 17 SSc patients and 17 healthy subjects that assessed the presence of coronary calcification by coronary CT, showed that signs of coronary atherosclerosis were present in 56.2% of SSc patients and in only 18.8% of age-, sex-, and race-matched controls.

Ho *et al*^[34] performed carotid duplex scanning and measurement of ankle brachial blood pressure index in 54 SSc patients and 43 control subjects that did not differ regarding cardiovascular risk factors. Their results showed that 64% of SSc patients had carotid artery disease compared with only 35% of the controls. In addition, SSc patients had a significantly higher prevalence (17%) of peripheral arterial disease. The results led to the conclusion that macrovascular disease is more common in SSc patient population. In addition, the mean intima media thickness, which is an indicator for the presence of atherosclerotic disease, has been shown to be either increased in SSc patients^[35] or unchanged^[36] as compared with healthy individuals.

The development of accelerated atherosclerosis in SSc is thought to be influenced by viral agents, immune reactions, anti-endothelial antibodies, or ischemia-reperfusion injury. Increased levels of C-reactive protein, homocysteine, von Willebrand factor, and vascular adhesion molecules, which are associated with the atherosclerotic process, as well as elevated and normal levels of lipids, have been reported in SSc^[29,37].

In a systematic review and meta-analysis of the literature, Au *et al*^[38] concluded that SSc patients are at an increased risk for atherosclerotic disease as compared

with healthy subjects. Microvascular disease is a pathognomonic feature of SSc as both vasospasm and structural alterations are present. Such alterations are thought to predict macrovascular atherosclerosis over time. However, the level of inflammation in SSc is lower than in rheumatoid arthritis and systemic lupus erythematosus. Thus, the atherosclerotic process may not be as aggressive and not easily detectable in small-number studies^[37].

Arrhythmias and conduction defects

Arrhythmias and conduction abnormalities are thought to be a result from conduction system fibrosis^[39,40] and myocardial fibrosis^[41]. Atrial and ventricular tachyarrhythmias result from myocardial fibrosis, whereas conduction defects and bradyarrhythmias are a consequence of conduction system fibrosis^[1].

Conduction system involvement is uncommon overall, rarely correlates with myocardial involvement, and is not usually clinically manifested^[39,40]. However, autopsy findings show that when fibrosis of the conduction tissues occurs, it most commonly affects the sinoatrial node^[39,40]. The most common clinical symptoms are dyspnea, palpitations, syncope. Of note, sudden death may also occur^[38].

At rest, normal electrocardiography has been recorded in over 50% of SSc patients, with an increase of arrhythmia rate noted during exercise^[41]. In 50 SSc patients, the most frequent abnormalities on the resting electrocardiogram were left anterior fascicular block (16%) and first-degree atrio-ventricular heart block (8%). The overall percentage of the abnormal findings was 32%. Of note, left bundle branch block and right bundle branch block with left anterior fascicular block were associated with abnormal left ventricular function, whereas isolated right bundle branch block or left anterior fascicular block were found in patients with normal left ventricular function^[41]. Twenty four-hour ambulatory continuous tape-recorded electrocardiograms demonstrated serious pathologic findings in a greater number of patients (62%): including supraventricular tachycardias (32%), conduction disturbances (14%), coupled ventricular extrasystoles (20%), and ventricular tachycardia (10%)^[42]. This same methodology also revealed conduction disturbances (such as sinus node dysfunction and first-degree heart block) and arrhythmias (*e.g.*, supraventricular tachycardia, atrial fibrillation, premature contractions from atrial or junctional origin, ventricular tachycardia, multifocal ventricular premature contractions) in 56.5% (26/46) of SSc patients^[43].

Supraventricular arrhythmias are considered to be more common in SSc patients, occurring in approximately two thirds of the cases, and much more frequent than ventricular tachyarrhythmias^[43]. Ferri *et al*^[44] also registered arrhythmias and conduction defects in a substantially higher proportion of SSc patients using 24-h Holter monitoring. In 53 SSc patients [34 with diffuse scleroderma and 19 with Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Telangiectasia syndrome (CREST)], rhythm and conduction abnormalities (*e.g.*,

conduction defects, supraventricular or ventricular arrhythmias and ST-T changes) were found in only 42% (22/53) on resting electrocardiogram. Using Holter monitoring, the number of detected conduction abnormalities increased from 10 to 16 patients, and transient ST-T changes increased from 2 to 18 patients. In addition, 48 patients had ventricular arrhythmias, with multiform ventricular premature beats in 21 (40%), pairs of runs of ventricular tachycardia in 15 (28%), and one or more runs of ventricular tachycardia in 7 (13%) cases. Furthermore, echocardiographic examination revealed asymmetric septal hypertrophy (10/53), impaired ventricular function (9/53), congestive cardiomyopathy (2/53), mitral prolapse (4/53), and pericardial effusion (3/53). Of note, multiform and/or repetitive ventricular premature beats occurred more frequently in patients with echocardiographic abnormalities, but were also present in patients who had normal findings on echocardiographic examination. It should be underlined, that the cardiac abnormalities did not correlate with the clinical variant of SSc (CREST syndrome or diffuse scleroderma), nor with other signs and symptoms of the disease.

Holter monitoring is therefore recommended in patients with symptoms of palpitations, lightheadedness, dizziness, or syncope, irrespective of the normal resting electrocardiogram. Exercise treadmill electrocardiogram may be helpful to identify exertional type arrhythmias. In all cases, a correlation with echocardiographic findings should be sought. Treatment protocols should follow the general guidelines in cardiology for management of the different forms of arrhythmias^[1].

Pericardial involvement

Pericardial abnormalities in SSc may manifest as fibrinous or fibrous pericarditis, pericardial adhesions, or pericardial effusion, and rarely as pericardial tamponade or constrictive pericarditis. Pericardial pathology is clinically apparent in over 5%-16% of the cases^[45]. The prevalence may be greater in SSc with limited cutaneous involvement (30%) *vs* patients with diffuse cutaneous form of the disease (16%)^[46]. At echocardiography, pericardial effusion can be detected in up to 41% of patients^[46], and in a larger proportion of cases (33%-72%) at autopsy^[45].

Pericardial involvement in SSc is usually clinically silent and benign. In the majority of cases, the presence of small pericardial effusion does not produce clinical symptoms and does not possess prognostic significance^[46]. Large hemodynamically significant pericardial effusions associated with heart failure may carry a poor prognosis and cause renal failure, probably due to the cortical renal hypoperfusion in the context of the large pericardial effusions and the administration of diuretics. Cardiac tamponade is rare and has a poor outcome. It should be emphasized that a small amount of rapidly accumulating pericardial fluid may cause tamponade because of the relative incapacity of the fibrotic pericardium for distension. Thus, close monitoring of SSc patients with acute pericarditis is recommended until complete resolution

of the symptoms, especially in the cases with coexisting myocardial involvement^[46]. Exudative pericarditis is easily diagnosed *via* echocardiography, which may be ordered after the findings on electrocardiogram (ST-T changes, low voltage) and chest X-ray (enlarged heart with a globular shape)^[46].

Pericardial effusions usually occur after the manifestations of other clinical features of SSc. Of note, large pericardial effusions, including those with development of tamponade, have been described prior to skin thickening and the establishment of the SSc diagnosis^[7,45,47,48]. Thus, SSc should be included in the diagnostic algorithm for the pericardial effusion of unknown origin. Pericardial effusions may also develop secondary to PAH or in the context of renal failure^[45].

Constrictive pericarditis presents as a right-sided heart failure with symptoms of shortness of breath, fatigue, anorexia, and wasting. Clinical manifestations may be in the context of both constrictive pericarditis and restriction due to myocardial fibrosis. Echocardiography, invasive measurement of LV and RV hemodynamic parameters, cardiac MRI and CT, may facilitate the differentiation. Diastolic septal bounce with increased respiratory variation in mitral inflow, discordance of peak left and right ventricular pressure at maximal inspiration, and enhanced and/or thickened pericardium on cardiac MRI, support the diagnosis of constrictive pericarditis. Of note, B-type natriuretic peptide (BNP) [and its cleavage product N-terminal pro BNP (NT-proBNP)], which is secreted from cardiomyocytes in response to atrial or ventricular wall stretch, and is increased in myocardial involvement, is normal or close to normal in constrictive pericarditis. Treatment includes diuretics, sodium and fluid restriction, and in selected cases, in the absence of contraindications (simultaneous presence of constrictive and restrictive pathologies and comorbidities), and pericardial stripping^[1].

The pathogenesis of pericardial effusion in SSc is thought to differ from rheumatoid arthritis and systemic lupus erythematosus. This notion is based on the findings that the pericardial fluid is noninflammatory by nature; auto-antibodies, immune complexes and complement depletion are absent. In addition, a general lack of response to corticosteroid treatment in scleroderma pericardial disease has been noted^[48]. At histological examination, nonspecific fibrotic pericardial thickening with adhesions and perivascular inflammatory cell infiltration have been found^[45].

Treatment

Treatment may include nonsteroidal anti-inflammatory drugs with close monitoring of renal function. Corticosteroids are considered to be of limited benefit in SSc-related pericardial disease^[45], but steroid-responsive cases also occur^[49], and corticosteroids may be life-saving in cases with associated myocarditis^[45]. Immunosuppressors may be indicated if profound inflammation is evident. Diuretics are considered in cases of heart failure but

should be used with caution due to the risk for development of renal failure^[45]. Pericardiocentesis is indicated in cases of life-threatening tamponade^[1].

SSc-related endocarditis

Valvular vegetations are considered to be rare manifestations in SSc. However, such lesions were found in 5 out of 28 autopsied SSc cases, including lesions of the mitral and tricuspid valve (alone or in combination), along with involvement of the chordae tendineae^[50], or the aortic valve^[51]. Nodular thickening of the mitral and aortic valves with regurgitation and mitral valve prolapse has also been noted^[45,52]. The clinical significance of such changes in SSc patients is unknown. Of note, endocarditis may occur in association with severe myocardial damage^[53].

Interestingly, embolisms in the brain and foot in SSc in the presence of mitral vegetation were found on echocardiography, and infective endocarditis was excluded on the basis of serial negative blood cultures and the absence of fever or known rheumatic valvular disease^[53].

SECONDARY CARDIAC COMPLICATIONS IN SSc

PAH

PAH is a syndrome resulting from restricted flow through the pulmonary arterial circulation with subsequent increased pulmonary vascular resistance and right heart failure^[54]. The prevalence of PAH in SSc is about 10%-12%^[55], varying between 4.9% and 26.7% depending on the applied diagnostic tools^[56]. PAH in SSc may be associated with pulmonary fibrosis, or may develop due to vascular narrowing or occlusion in cases with or without minimal pulmonary fibrosis. Pulmonary fibrosis is found in more than one third of SSc patients with either the diffuse or limited form of the disease. Post-mortem examinations revealed alveolar, interstitial, peribronchial and pleural fibrosis. PAH in the context of pulmonary fibrosis is usually of moderate degree and is characterized with relatively slow progression that develops as a result of the gradually increasing resistance of the pulmonary vasculature^[57,58]. PAH in SSc patients with minimal or no pulmonary fibrosis is a severe complication, and is a consequence of narrowing or occlusion of small pulmonary arteries caused by smooth muscle hypertrophy, intimal hyperplasia, vascular inflammation, and thrombosis *in situ*. Dyspnea from normal exercise tolerance to oxygen dependency progresses over 6-12 mo, with a mean survival of two years, whereas PAH in the context of lung fibrosis progresses more slowly, over two to ten years^[54,57,59,60].

Of note, isolated PAH, in the absence of pulmonary fibrosis, is more frequent in the limited cutaneous form of SSc (45%) than in the form with diffuse cutaneous involvement (26%)^[61]. Histological evidence for PAH at autopsy is also more frequent (over 65%-80% of cases). These data suggest a substantial prevalence of mild and moderate forms of PAH in SSc^[54,62]. PAH is considered

to be one of the most important factors contributing to the increased morbidity and mortality in SSc^[63]. The high incidence and prevalence of PAH in SSc, its poor prognosis, and the efficacy of the new evidence-based treatment that improves survival, stimulated the recommendation of an obligatory regular screening of pulmonary arterial pressure (PAP) in SSc patients.

Clinical signs of PAH include dyspnea on exertion, fatigue, chest pain, dizziness, palpitations, and edema at the lower extremities. Upon physical examination, an accentuated pulmonary component of the second heart sound, gallop, and pansystolic murmur of tricuspid regurgitation may be found, as well as features of right heart failure in advanced cases^[56]. The chest X-ray and electrocardiogram may reveal signs suggestive of PAH, mainly in the later stages, such as an enlarged pulmonary artery, attenuation of peripheral pulmonary vascular markings (at the chest X-ray), and peaked P wave ≥ 2.5 mm in leads II, III and aVF^[54,56]. If PAH is suspected, a transthoracic Doppler echocardiography is recommended^[54,56]. At echocardiography, PAH is defined as mean PAP > 25 mmHg at rest, > 30 mmHg during exercise, or systolic pulmonary pressure > 40 mmHg. Clues to diagnosis can be an elevated tricuspid regurgitation velocity (TRV) jet above 2.8 m/s, or a dilated right ventricle or atrium^[64]. The decreasing carbon monoxide diffusing capacity (DL_{co}) is a marker of pulmonary vascular disease and is standardly used in the diagnostic approach when PAH is suspected. Of note, it is associated with poor prognosis. CT and MRI may also be used to assess right ventricular mass, volume, and function. At MRI, the ratio of septal curvature, right ventricular ejection fraction, and right ventricular volume may be evaluated^[54].

All patients that are suspected of having PAH after noninvasive evaluation should undergo right heart catheterization (RHC) prior to therapy initiation. This method is the gold standard for diagnosing PAH, and allows for the measurement of the transpulmonary gradient (PAP mean wedge), which was found to be significantly elevated only in PAH patients, but not in patients whose pulmonary hypertension was due to increased cardiac output, left heart myocardial or valvular disease^[54,65]. A more reliable diagnostic parameter for PAH is pulmonary vascular resistance (PVR), which reflects the influence of transpulmonary gradient and cardiac output and is only elevated if the vascular obstruction occurs within the pre-capillary pulmonary circulation. However, PVR can also be elevated in patients with valve disease or left ventricular heart disease^[56]. Consequently, PAH is a diagnosis of exclusion. In the absence of lung disease, thromboembolism, left ventricular or valve pathology, the diagnosis of PAH requires both a mean PAP greater than 25 mmHg and a PVR greater than 3 Wood units with a pulmonary capillary wedge pressure < 15 mmHg (for exclusion of left heart disease)^[54,65]. In addition, BNP and NT-pro-BNP are promising screening parameters in SSc-related PAH, as increased levels correlate with disease severity

Table 2 Therapies for systemic sclerosis-related pulmonary arterial hypertension^[64-82]

Therapeutic approach	Dosage/comments
Prostanoids	
Epoprostenol: a prostacyclin with a very short half-life of 6 min; unstable at pH values below 10.5, requires intravenous administration ^[54,68]	Starting dose is 1-2 ng/kg per minute, gradually increased up to 25-40 ng/kg per minute
Treprostinil: an epoprostenol analogue with a half-life of 4.5 h, given as a continuous subcutaneous or intravenous infusion in patients with PAH from functional class II, III and IV ^[54,69]	10-20 ng/kg per minute
Iloprost: a chemically stable prostacyclin analogue with a longer half-life (20-25 min), given as a continuous intravenous infusion for 6-8 h ^[70]	0.5-3.0 ng/kg per minute
Beraprost: the first oral prostacyclin analogue with vasodilative and antiplatelet action and a half-life of approximately 1 h, indicated in primary and secondary PAH ^[72,73]	20 µg qid, may be increased by 20 µg/wk. The maximum allowed dose was 120 µg qid with a mean of 80 µg qid
Prostaglandins for inhalation	
Iloprost: inhalation has a pulmonary vasodilative potency similar to prostacyclin with longer effects (30-90 vs 15 min); effective in patients with severe PAH functional class III and IV ^[71]	2.5 or 5.0 mg six or nine times/d; median inhaled dose, 30 µg/d
Endothelin receptor antagonists	
Bosentan: the first drug from this group that was approved for treatment of PAH associated with systemic rheumatic diseases in the United States, Canada, Switzerland and European Union; indicated for PAH functional classes II, III and IV ^[74,75]	62.5 mg bid for 4 wk before titration up to 125-250 mg bid
Sitaxsentan: highly selective endothelin receptor antagonist with a long duration of action; high specificity for type A over type B receptors (6500:1) leads to blockade of the vasoconstrictory effect of endothelin-1 and maintenance of the vasodilative and clearance function of type B receptors ^[76]	50-100 mg/d
Ambrisentan: antagonist selective for type A over type B endothelin receptors (4000:1) ^[77]	2.5-10 mg
PDE inhibitors	
(PDE degrades cGMP, which mediates the effect of nitric oxide—a potent vasodilator and an inhibitor of platelet activation and vascular smooth muscle)	
Sildenafil: a specific inhibitor of the PDE-5 isoform present in large amounts in the lung ^[78]	20 mg 3 tid
Vardenafil: a PDE-5 inhibitor ^[80]	20 mg 3 tid
Tadalafil: a specific inhibitor of PDE-5 with a longer half-life (17.5 vs 3.8 h for sildenafil) ^[79]	20 mg 3 tid
Combination therapy	
(oral with inhaled and intravenous drugs)	
Sildenafil with intravenous epoprostenol Sildenafil and bosentan ^[81]	
Others	
Sodium consumption needs to be restricted to 2400 mg/d in patients with right ventricular failure; digoxin and diuretics when indicated	Saturation < 90% at rest or with exercise; Titration to an international normalized ratio of 1.5-2.5
Surgical options: atrial septostomy, single and double lung transplantation and combined heart and lung transplantation are ultimate therapeutic options in patients with end-stage disease ^[54]	
Routine immunization against influenza and pneumococcal pneumonia	
Oxygen therapy	
Anticoagulation therapy: (warfarin) in advanced stages with continuous intravenous therapy and in the absence of contraindications	
Although inflammation plays a significant role in the development and the progression of PAH, immunosuppression is not a common treatment, as systemic sclerosis-PAH is usually quite refractory to immunosuppressive drugs ^[82] . However, immunosuppressive treatment has led to improvements in some cases of PAH in other connective tissue diseases (e.g., systemic lupus erythematosus, primary Sjögren syndrome)	

PDE: Phosphodiesterase; PAH: Pulmonary arterial hypertension.

and predict survival^[54,64,65].

Treatment

The general therapeutic algorithm in SSc-PAH is summarized in Table 2. During RHC, vasodilator testing is performed in order to predict the therapeutic response. The response is defined as a reduction ≥ 10 mmHg to a mean PAP ≤ 40 mmHg, without a decrease in cardiac output^[54]. It includes administration of inhaled nitric oxide, intravenous epoprostenol or intravenous adenosine. It has been found that responders are more likely to have a sustained beneficial response to oral calcium channel blockers (long-acting nifedipine, diltiazem and amlodipine) than non-responders^[54,83-85]. Verapamil should be avoided because of its potential for negative inotropic

effects. High doses of calcium-channel blockers may improve survival in patients with primary PAH who respond with reductions in pulmonary arterial pressure and vascular resistance^[86].

SSc-associated PAH historically had a poor prognosis with a one-year survival rate of 45%^[55,87]. Survival, though still poor, has significantly increased with modern therapies such as prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors, which can improve pulmonary hemodynamics and functional capacity in patients with PAH in the context of connective tissue diseases. A six-year follow-up (2001-2006) of 315 patients with SSc-related PAH from the United Kingdom National registry has demonstrated one-, two- and three-year survival rates of 78%, 58% and 47%, respectively^[55,88,89].

Table 3 Criteria for definition of hypertensive scleroderma renal crisis

In the presence of limited or diffuse cutaneous scleroderma renal crisis:

A new onset of blood pressure > 150/85 mmHg obtained at least twice over a 24 h period. This blood pressure is defined as significant hypertension by the New York Heart Association

A documented decrease in renal function as defined by a decrement of at least 30% in the calculated glomerular filtration rate. When possible, initial results should be confirmed by a repeat serum creatinine concentration and recalculation of the glomerular filtration rate

To corroborate further the occurrence of acute renal crisis, it would be desirable to have any of the following (if available):

Microangiopathic hemolytic anemia on blood smear

Retinopathy typical of acute hypertensive crisis

New onset of urinary red blood cells (excluding other causes)

Flash pulmonary edema

Oliguria or anuria

Renal biopsy showing characteristic changes

Renal biopsy showing an alternative cause excludes the case from classification as scleroderma renal crisis

Early diagnosis of SSc-PAH and early subsequent intervention are essential for delaying disease progression. Early detection of PAH, when patients have few or no symptoms (*i.e.*, functional class I and II), is challenging. Available data broadly support annual screening of all SSc patients with and without symptoms. Patients with SSc who are at high risk for development of PAH are those with DL_{CO} < 60% predicted or who have declining DL_{CO} (*e.g.*, 20% decrease over a one-year period). Doppler echocardiography conducted at rest is considered to be the method of choice for PAH screening. For patients with TRV > 3.4 m/s (corresponding to a systolic PAP > 50 mmHg) or with a TRV between 2.9 and 3.4 m/s (corresponding to a systolic PAP between 34 and 49 mmHg) in the presence of other signs suggestive of PAH, non-invasive workup is recommended, including biomarkers, high-resolution CT and decision for confirmation of PAH *via* RHC^[90,91]. In the recently performed DETECT study aimed to define recommendations for earlier detection of SSc-related PAH, six variables were determined to guide to the echocardiography, including forced vital capacity/DL_{CO} (% predicted), presence of current/past telangiectasias, serum anticentromere antibodies, serum NT-proBNP, serum urate and right-axis deviation on electrocardiogram. TRV and right atrium area are evaluated in order to define the necessity of RHC for confirmation of PAH. It has been postulated that using TRV alone would fail to diagnose 20% of PAH patients when using a PAH suspicion threshold of ≥ 2.5 m/s, 36% when using a threshold of > 2.8 m/s, and 63% when using a threshold of > 3.4 m/s^[92].

Cardiac symptoms in severe scleroderma-related kidney involvement

A severe systemic hypertension due to SRC may trigger the development of systolic dysfunction and congestive heart failure^[4]. SRC occurs in over 10% of SSc patients, in 10%-25% in the subgroup of SSc patients with diffuse cutaneous involvement, and in only 1%-2% of those with a limited form of the disease^[1,93]. Most patients have a profound elevation of blood pressure at the onset of SRC; 90% have a pressure > 150/90 mmHg, and 30% have a diastolic pressure > 120 mmHg. Of note, an increase of 20 mmHg in blood pressure values may

be significant for a particular patient even though the values may still be in the normal range, and this also may represent a renal crisis. Only 10% of SRC are clinically associated with normal values of blood pressure. SRC is the most important renal complication in SSc based on vasculopathy, fibrosis and autoimmunity with a central role of the renin-angiotensin axis, as demonstrated by the striking clinical efficacy of ACE inhibitors^[1]. The diagnosis of hypertensive SRC is established on the basis of recently developed criteria (Table 3)^[94]. Factors for predicting the development of SRC include diffuse cutaneous involvement, rapid progression of skin involvement, disease symptoms for less than four years, presence of anti-RNA polymerase III antibody, new anemia, new cardiac events (pericardial effusion, congestive heart failure), and antecedent high-dose corticosteroids. Of note, previous blood pressure elevations, stable, mildly elevated serum creatinine, abnormal urine analysis, anti-topoisomerase and anticentromere antibodies, or pathologic findings in renal blood vessels are not predictive for the development of SRC^[1]. The clinical features include headache, breathlessness, dizziness, syncope. All SSc patients should be encouraged to check their blood pressure if such clinical symptoms are present. It is recommended that the SSc patients with predictive factors for the development of SRC should monitor their blood pressure twice weekly^[1].

Hypertension that occurs prior to the onset of SSc is usually essential, while those that develop after the onset of the disease could be either essential hypertension or, more likely, SSc-related^[95]. ACE inhibition is the cornerstone for the treatment of hypertension in SRC. ACE inhibitors should immediately be started once the diagnosis is established, or the dose increased if the patient is already taking them. ACE inhibitor resistance is a frequent finding in SSc patients. In such cases, the dose must be gradually increased to a maximum level. Early reduction or discontinuation of ACE inhibitors should be avoided. Denton *et al*^[96] recommend doubling the dose every 24 h, though deterioration of renal function may continue in this period. Frequently, it takes several days for blood pressure to fall to normal. In cases of insufficient blood pressure decrease, the authors recommend adding angiotensin receptor blockers, calcium channel blockers, doxazosin or clonidine^[96]. Beta blockers are contraindicated in

SRC due to their effect on peripheral circulation. Parenteral antihypertensives are not generally recommended, although nitrate infusion is sometimes indicated for the management of pulmonary edema^[1]. The aim of the antihypertensive treatment is to achieve pre-SRC values of blood pressure. The mean decrease per 24 h should be over 20 mmHg for the systolic and 10 mmHg for the diastolic blood pressure. Prolonged periods of hypotension should be avoided^[96]. If renal replacement is required, hemofiltration and hemodialysis are used depending on the hemodynamic stability and availability of the center. More than half of the patients who have undergone dialysis were able to discontinue it in 3-18 mo. Over 20% of the cases require chronic dialysis and 20% had an early death^[1].

SRC has been a leading cause for increased mortality in SSc, though survival has dramatically improved with the use of ACE inhibitors. Patients with SRC who received ACE inhibitors had an impressive one-year survival of 76% and a five-year survival of 65%, compared with 15% one-year survival and 10% five-year survival of patients not receiving ACE inhibitors, despite other aggressive antihypertensive treatment^[97,98]. The use of ACE inhibitors should continue indefinitely because recurrences occur years after the initial event when ACE inhibitors are discontinued^[1]. Prophylactic use of ACE inhibitors prior to SRC does not prevent its development^[1,99].

EVALUATION OF SSc PATIENTS WITH CARDIAC INVOLVEMENT

Laboratory investigations

Screening for biologic markers of possible cardiac dysfunction may be beneficial. One such laboratory marker is BNP, which is secreted from cardiomyocytes in response to atrial or ventricular wall stretch. Annual measurement of BNP is thought to be beneficial, as plasma concentrations correlate with the risk of death and cardiovascular events. BNP originates from the precursor protein pre-proBNP, which is first cleaved to proBNP, and then to active BNP and NT-proBNP. Both BNP and NT-proBNP can be measured in clinical practice, but the advantages of the latter are its longer half-life and increased stability. Of note, their levels vary according to gender and age. These markers are used for the screening of overall cardiovascular pathology in SSc, including PAH. There is not sufficient evidence that one natriuretic peptide is superior to another in this regard. The upper normal limits are 125 pg/mL for NT-proBNP and 60 pg/mL for BNP^[1,13,100,101]. Levels may be elevated in primary scleroderma-related myocardial involvement, as well as in pulmonary or systemic hypertension and in conventional concomitant cardiac diseases, such as acute and chronic coronary artery disease, left and right ventricular systolic and diastolic dysfunction, valvular heart disease, atrial arrhythmias, and heart failure^[1,13].

It should be emphasized that NT-proBNP is not cleared by natriuretic peptide clearance receptors and is

primarily excreted by the kidney. Thus, renal dysfunction is more likely to cause its elevation with less effect on BNP level. Of note, a number of noncardiac conditions may increase the level of natriuretic peptides, such as older age, female gender, weight loss, renal insufficiency, sepsis, pulmonary embolism, anemia, cirrhosis, corticosteroid administration, hyperthyroidism, malignancies, or central nervous system injury. On the other hand, factors such as obesity, constrictive pericarditis, pulmonary edema, and some cardiac medications (ACE inhibitors, angiotensin receptor blockers, beta blockers, diuretics, spironolactone) are associated with normal or decreased natriuretic peptide levels^[1].

Other laboratory markers that have been investigated together with NT-pro-BNP to evaluate a subclinical cardiac involvement in SSc and have shown significantly higher levels as compared with controls, are ischaemia modified albumin, high-sensitivity C-reactive protein, and Erythrocyte Sedimentation Rate. No significant differences have been detected for ischemia modified albumin and NT-pro-BNP levels between the limited and diffuse cutaneous forms of SSc. Ischaemia modified albumin is thought to appear in different conditions of local or generalized hypoxia and thus is not a specific cardiac marker^[101].

Troponin has not been found to be elevated in SSc despite myocyte loss and myocardial fibrosis. Thus, when elevated troponin is present, myopericarditis or non-scleroderma cardiovascular disease, such as coronary syndrome or pulmonary embolism, should be suspected^[1,101].

Instrumental investigations

A resting electrocardiogram is not sufficient to diagnose rhythm and conduction disturbances in SSc. Thus, when clinical signs like palpitations or syncope are present, 24-h Holter monitoring is indicated. Holter monitoring has demonstrated good sensitivity to detect arrhythmias and conduction abnormalities in a significantly higher percentage of patients as compared with the resting electrocardiography^[44], and should be included in the diagnostic algorithm of SSc patients with symptoms of palpitations, syncope, or dyspnea with unknown origin. New devices of Holter electrocardiographs may collect data for up to 14 d. In patients with less frequent symptoms, long-term Holter assessment (usually for a 30-d period) may be necessary. Of note, there are implantable monitors, which can detect arrhythmias indefinitely and may be also used in difficult cases^[1]. Exercise treadmill electrocardiogram may be helpful to identify the exertional type of arrhythmia^[1].

A transthoracic echocardiography should be included in the routine diagnostic screening of SSc patients^[1,44]. Of note, normal electrocardiographic findings were associated with normal left ventricular function at rest^[40]. Echocardiography allows measurement of atrial and ventricular dimensions, volumes (including ejection fraction), diagnosing of systolic and diastolic dysfunction, pericardial, valvular disease, and pulmonary hypertension^[1]. TDI

is a modern echographic method that allows the accurate measurement of regional and global LV and RV function, and the inclusion of this technique has improved the accuracy and reproducibility of standard echocardiography^[11].

Nuclear imaging, such as thallium-201 SPECT and PET scanning, are sensitive tools for detection of microvascular abnormalities in SSc-related myocardial disease. Detection of subendocardial ischemia by nuclear imaging is limited and inferior as compared with cardiac MRI^[1]. Cardiac MRI with or without contrast enhancement is a modern imaging modality that detects both structural and functional cardiac abnormalities in SSc patients with significantly superior sensitivity as compared with echocardiography (75% vs 48% detection rate in a cohort of 53 SSc patients)^[10]. Cardiac MRI gives an opportunity for quantitative assessment of myocardial perfusion and the effect of vasodilators^[3]. Chest CT may be used for combined assessment of lung and cardiac involvement in SSc. Cardiac CT and MRI are valuable techniques for detection of pericardial thickness and inflammation^[1].

Cardiac catheterization is indicated in SSc for diagnosis of PAH, constrictive pericarditis, cardiac tamponade and epicardial coronary artery disease, for performing endomyocardial biopsy in cases of suspected infiltrative cardiac disease^[1].

CONCLUSION

Cardiac involvement in SSc may present with various manifestations and is an indicator of a poor prognosis. The rheumatologists should be acquainted with the different forms of primary and secondary cardiac involvement in SSc and the necessity for screening for the detection of subclinical cases *via* modern sensitive tools, as early diagnosis and treatment are crucial for a positive outcome.

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Serum creatinine role in predicting outcome after cardiac surgery beyond acute kidney injury

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and prediction of AKI, but also the most important predictor of outcome after cardiac surgery, including mortality and morbidity as well as hospital length of stay.

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Abstract

Serum creatinine is still the most important determinant in the assessment of perioperative renal function and in the prediction of adverse outcome in cardiac surgery. Many biomarkers have been studied to date; still, there is no surrogate for serum creatinine measurement in clinical practice because it is feasible and inexpensive. High levels of serum creatinine and its equivalents have been the most important preoperative risk factor for postoperative renal injury. Moreover, creatinine is the mainstay in predicting risk models and risk factor reduction has enhanced its importance in outcome prediction. The future perspective is the development of new definitions and novel tools for the early diagnosis of acute kidney injury largely based on serum creatinine and a panel of novel biomarkers.

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Key words: Creatinine; Acute kidney injury; Cardiac surgery; Outcome; Biomarker

Core tip: This manuscript aims to review the latest achievements in the diagnosis and treatment of acute kidney injury (AKI). Despite much progress in recent years, especially in the development of novel biomarkers, serum creatinine still plays the major role. Creatinine is not only the mainstay of definition, diagnosis

INTRODUCTION

Creatinine is an important determinant in cardiac surgery. Rise in the level of serum creatinine has a significant impact on surgical outcome. Acute kidney injury (AKI) is basically defined by perioperative changes in serum creatinine level. Even minimal changes in serum creatinine not high enough to be defined as AKI worsen the outcome of patients who undergo cardiac surgery. Sensitivity of serum creatinine is low and its response to renal insult is slow and late. However, serum creatinine level still constitutes the main measure for the assessment of renal function thanks to the simplicity and availability of its measurement. Similarly, serum creatinine is the cornerstone of the consensus definitions of AKI. Indeed, an acronym for Risk of renal failure, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage renal failure (RIFLE), acute kidney injury network (AKIN) and Kidney Disease: Improving Global Outcomes (KDIGO) all use creatinine for grading the severity of AKI^[1,2]. The principal role of creatinine as a main predicting factor in the scoring systems for risk estimation is well known^[3]. Creatinine has, therefore, been included in the first three important risk factors for mortality after cardiac surgery by newer prediction scores^[4].

With little tolerance, we assume an abrupt rise in serum creatinine as acute kidney injury (AKI). Due to

the unique characteristics and specifications of AKI that occur after cardiac surgery, it has been called cardiac surgery associated AKI (CSA-AKI). In recent years, many investigations have been performed to find answers to key questions on the prevention and treatment of CSA-AKI in the perioperative period. Numerous studies have been performed and are underway with their focus on the CSA-AKI^[2,5] and there are promising results, especially in prophylactic management. However, recruitment of patients with minimum risk of AKI for clinical trials on CSA-AKI treatment is the main reason why most of these studies lack the sufficient power to be conclusive^[2,5]. Furthermore, inconsistency in the definition of AKI between different studies makes it difficult to analyze the results of these studies in meta-analyses^[5,6].

This review covers the following: (1) association of serum creatinine with cardiac surgery-associated mortality and morbidity; (2) serum creatinine role in diagnosis of cardiac surgery-associated acute kidney injury; (3) risk factors for high perioperative serum creatinine; (4) risk models for AKI after cardiac surgery; (5) creatinine and the outcome prediction in cardiac surgery; and (6) prevention and treatment on the horizon.

ASSOCIATION OF SERUM CREATININE WITH CARDIAC SURGERY-ASSOCIATED MORTALITY AND MORBIDITY

The development of postoperative AKI has been recognized as the strongest risk factor for death in patients undergoing cardiac surgery^[7]. It has been shown that AKI occurs in up to 40% of patients undergoing cardiac surgery^[2]. As much as the incidence is rare (1% to 5%), mortality among patients with AKI who require renal replacement therapy (RRT) or become dialysis dependent is more than 50% and approaches 80% in patients who need dialysis, while the overall mortality rate after cardiac surgery hardly exceeds 8%^[7-9].

AKI increases postoperative morbidity, length of stay in the intensive care unit (ICU) and hospital and costs of care^[10]. High level of preoperative serum creatinine is associated with higher risk of RRT and need for dialysis after cardiac surgery^[11,12]. Even minimal changes in serum creatinine increase postoperative mortality significantly. Indeed, 30 d mortality was reported to be 2.8 and 18.6 fold higher with up to a 0.5 mg/dL and more than 0.5 g/dL creatinine rise, respectively, compared to no change in a group of patients who underwent cardiac surgery^[13]. The risk of AKI increases in valvular and combined surgery compared to myocardial revascularization two to four times, respectively^[11,14,15].

It has been indicated repeatedly in different studies that serum creatinine rise after cardiac surgery is followed by long-term chronic kidney disease (CKD) and mortality^[16-19]. Moreover, higher degrees of preoperative kidney insufficiency are accompanied by a proportionally higher risk of CSA-AKI and need for RRT^[20]. Pathophysiologi-

cal studies indicate that cardiac patients with AKI are more likely to have progressive renal changes beyond the acute episode even after reduction of serum creatinine to normal levels^[19,21,22].

AKI has been divided into pre-renal, renal and post-renal with regards to etiology. In surgical patients, pre-renal etiology, followed by renal etiology, is the most common cause of AKI^[23]. As volume changes are common during cardiac surgery, CSA-AKI can be divided into volume responsive and non-volume responsive which usually matches pre-renal and renal etiologies. Renal etiology of CSA-AKI is caused by various factors, including ischemia and ischemia-reperfusion injury, inflammation and oxidative stress, exogenous and endogenous toxins, metabolic abnormalities and neurohormonal activation^[24]. They can briefly be divided into hemodynamic, inflammatory and nephrotoxic factors^[25,26].

SERUM CREATININE ROLE IN DIAGNOSIS OF CSA-AKI

In this section, we discuss that new equations have improved the calculation of glomerular filtration rate estimation (eGFR), especially in people with suboptimal kidney function and near normal real GFR. Moreover, new consensus systems are focused on more accurate practical definitions of AKI so that they can be better tools for outcome prediction. Nonetheless, there are obstacles to employing these formulas and definitions in cardiac surgery and creatinine still rules supreme.

Kidney impairment after cardiac surgery is acute in onset and most probably occurs in patients without a previous history of renal insufficiency. However, conventional formulas for eGFR have been released by studies on patients with renal impairment. Similarly, well-known definitions of AKI have been developed by analyzing data from patients with previous CKD. Paradoxically, most of the studies on AKI diagnosis and management after cardiac surgery have been performed in people without CKD, while we know CKD is the most important predictor of postoperative AKI. This shows how challenging it is to study the most important complication of cardiac surgery.

Creatinine clearance and eGFR methods

Serum creatinine has been used to determine GFR for a long time. Even the diagnosis and staging of CKD has been made through serum creatinine measurement. However, the serum concentration of creatinine is affected by factors such as age, gender, ethnicity, diet, muscle mass and medication. Moreover, creatinine will not be higher than the normal range until 50% of renal function is lost^[27]. Direct measurement of GFR with inulin or radio-nuclides is expensive and complex and thus not suitable for routine use. Furthermore, the older method of 24 h urine sampling for the measurement of creatinine clearance is not easy to perform and the results are biased owing to some tubular secretion of creatinine that causes

up to 40% overestimation of GFR compared to inulin clearance^[27]. That is why better tools for the assessment of GFR are required.

There are several creatinine-based formulas for the estimation of GFR that are widely used in research and clinical practice. The Cockcroft-Gault formula, named after the two scientists who developed it in 1976, is the most common surrogate for creatinine clearance in the estimation of GFR^[28]. This formula employs age and weight as well as gender to calculate eGFR. The formula is useful due to simplicity and ease of calculation and it underscores the importance of age in estimating GFR: for the same level of creatinine, eGFR decreases to half at age 80 compared to age 20. However, the use of this simple equation in obese patients is not possible. Accordingly, ideal body weight, which is calculated taking height into account, is utilized in this group of people. Similarly, using adjusted body weight again while considering the role of height improves the GFR estimation in the elderly^[29]. These shortcomings limit its application in the laboratory to report creatinine clearance.

Another common formula was developed by the Modification of Diet in Renal Disease (MDRD) Study Group in 1999^[30]. It was simplified in 2002 by omitting albumin and blood urea nitrogen to a 4-variable MDRD which estimates GFR using the variables of age, gender, race and serum creatinine^[31]. Laboratories use this formula to report eGFR. This formula estimates GFR more precisely in patients with CKD. Nevertheless, both 6-variable and 4-variable MDRDs underestimate GFR in healthy individuals with creatinine clearance more than 60 mL/min. Furthermore, compared to the Cockcroft-Gault equation, MDRD do not adjust for body mass index and thus underestimates GFR in obese and overestimates GFR in underweight people^[32,33].

The most important shortcoming of both Cockcroft-Gault and MDRD equations is their development in patients with CKD. What is more, it has been shown that both formulas have lower precision in people with normal GFR^[33-35]. Cockcroft-Gault overestimates and MDRD underestimates GFR in this group of healthy population^[36]. Renal insufficiency in cardiac surgery is acute in onset and most probably in patients without any history of CKD. These formulas may, therefore, not be as useful in this group of patients^[37]. To overcome this problem, the CKD-epidemiology collaboration (CKD-EPI) developed a new formula in 2009. This equation is superior to MDRD when GFR is more than 60 mL/min. Unlike the other two formulas, CKD-EPI was developed through several studies in populations with suboptimal renal function^[38]. Advantageous in the CKD-EPI equation is its probable improved cardiovascular risk prediction compared to MDRD in a middle-age population^[39]. Findings in previous studies will probably need revision through a new formula^[40].

Development of new equations and making modifications to the available ones reflect the attempts to make eGFR an ideal surrogate for real GFR as much as possible. However, the closer we get to an accurate estimate

of GFR, the farther we get from a clinically more practical tool. The most important drawback to employing these formulas in clinical practice is the fact that we cannot find a formula to fit all clinical conditions. Accuracy of eGFR is compromised when the clinical condition is different from the populations from which the equations were derived. Malnutrition or reduction in muscle mass from illness or amputation, extremes of muscle mass and diet (such as vegetarians), different ethnicities from those included in studies used for the development of the equations, or changes in the non-GFR determinants over time are the most probable determinants of large differences between real and estimated GFR^[27,34].

A newer concept is to add laboratory parameters that are not dependent on body muscle mass and nutrition so as to obtain a better estimation of GFR. Using cystatin C, an index of glomerular function, is believed to be promising in different investigations in adults and children^[34,41,42]. There are even equations based on cystatin C to calculate GFR^[42,43]. However, cystatin C needs adjustment for age, gender and race, although adjusted cystatin C is probably superior to adjusted creatinine in developed equations^[44]. Moreover, the lack of an international standard to calibrate cystatin C limits the use of these equations. More to the point, we do not know whether the routine use of cystatin C merits its cost as there is no evidence that it improves outcome significantly^[45].

Preoperative creatinine and occult renal insufficiency

Discussion on preoperative creatinine revolves around the most important risk factor for CSA-AKI which is previous renal insufficiency^[8,46]. Nevertheless, no unique level of serum creatinine as a threshold for renal insufficiency has been defined^[47]. Predictor models for AKI are also not consistent: although most of them have reported preoperative renal insufficiency as a risk factor, their definitions for renal insufficiency are largely diverse from baseline creatinine of 1.5 mg/dL and eGFR of 60 mL/min as cut off points for dialysis dependency^[48]. This holds true for most of the predictor models of outcome in cardiac surgery that have included preoperative renal insufficiency as a predictor^[3,4,49]. Proteinuria, the most prevalent parameter used in the definition of CKD, is also absent in most of them due to a lack of data on urinalysis^[5].

There is no debate on patients who are dialysis dependent or need renal replacement therapy. We recognize these problems as kidney disease. The most challenging are the patients whose serum creatinine level is within normal range but their real GFR or eGFR is low. We call this condition occult renal insufficiency and it is usually defined as eGFR < 60 mL/min when creatinine is in normal range. Several studies have shown that the incidence of morbidity and mortality after cardiac surgery is higher in patients with occult renal insufficiency^[50-53].

AKI definition systems: RIFLE, AKIN and KDIGO

Despite the recognized importance of AKI, one of the major problems in conducting studies on the subject is

Table 1 Definition and classification for acute kidney injury

	Serum creatinine/GFR criteria	Urine output criteria
RIFLE classification		
Definition	SCr rise ≥ 1.5 times baseline or GFR decrease $> 25\%$ within 7 d	
Staging	R (Risk) SCr rise up to 2 times baseline or GFR decrease $> 25\%$	< 0.5 mL/kg per hour for ≥ 6 h
	I (Injury) SCr rise up to 3 times baseline or GFR decrease $> 50\%$	< 0.5 mL/kg per hour for ≥ 12 h
	F (Failure) SCr rise 3 times baseline or more or GFR decrease $> 75\%$ or absolute SCr ≥ 4 mg/dL with acute rise ≥ 0.5 mg/dL	< 0.5 mL/kg per hour for ≥ 24 h or anuria ≥ 12 h
	L (Loss) persistent AKI > 4 wk, need for RRT	
	E (ESRD) persistent loss > 3 mo, need for dialysis	
AKIN classification		
Definition	SCr rise ≥ 1.5 times baseline or ≥ 0.3 mg/dL within 48 h	
Staging	1 SCr rise up to 2 times baseline or ≥ 0.3 mg/dL	< 0.5 mL/kg per hour for ≥ 6 h
	2 SCr rise up to 3 times baseline	< 0.5 mL/kg per hour for ≥ 12 h
	3 SCr rise 3 times baseline or more or absolute SCr ≥ 4 mg/dL with acute rise ≥ 0.5 mg/dL or need for RRT	< 0.3 mL/kg per hour for ≥ 24 h or anuria ≥ 12 h
KDIGO classification		
Definition	SCr rise ≥ 1.5 times baseline within seven days or ≥ 0.3 mg/dL within 48 h or oliguria	
Staging	1 SCr rise up to 2 times baseline or ≥ 0.3 mg/dL	
	2 SCr rise up to 3 times baseline	
	3 SCr rise 3 times baseline or more or absolute SCr ≥ 4 mg/dL with acute rise ≥ 0.5 mg/dL or need for RRT	

GFR: Glomerular filtration rate; AKIN: Acute Kidney Injury Network; KDIGO: Kidney Disease: Improving Global Outcomes; RIFLE: An acronym for Risk of renal failure, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage renal failure; SCr: Serum creatinine; AKI: Acute kidney injury; RRT: Renal replacement therapy.

the lack of consensus regarding the diagnosis as there are more than 30 different definitions for AKI^[47]. In the past decade, several consensus systems have been introduced to define AKI uniformly in different studies. Perioperative changes in the serum concentration of creatinine are the cornerstone of the definition in these systems. In 2004, the RIFLE criteria were proposed by the Acute Dialysis Quality Initiative group^[47].

A revised version of the RIFLE criteria was suggested by the AKIN group in 2007. There are four main changes in AKIN compared to RIFLE (Table 1): GFR changes have been omitted from the definition system; time period of seven days for creatinine changes has been replaced by 48 h; creatinine changes as low as 0.3 mg/dL is the lowest measure to be considered as AKI; and the two outcome determinants in RIFLE (loss and end stage) are deleted to define AKI in three stages^[54].

Following the establishment of the AKIN scoring

system, the resultant debate over the supremacy of each criterion prompted comparative research^[55-60], which disclosed that AKIN was not more efficient than RIFLE and that some authors still preferred to employ RIFLE with some modifications^[55]. Modified RIFLE stages anyone who needs RRT in category F (failure) regardless of the level of serum creatinine. A recent study performed with this method reported an incidence of 14% for AKI and showed that CSA-AKI aggravated short and long term outcomes in cardiac patients^[19]. Nevertheless, a large survey of 1881 patients by Bastin *et al*^[61] indicated that the incidence of AKI with both AKIN and RIFLE criteria was mostly equal (25.9% and 24.9%, respectively), but hospital mortality was predicted more precisely by AKIN. Another dispute was over the sensitivity of the two definitions insofar as whether or not the designated thresholds sufficiently diagnose all the cases of renal impairment. Studies have shown that there are concerns about the adequacy of the AKIN and RIFLE criteria inasmuch as that by the current standards, some AKI cases may be left undiagnosed. Lassnigg *et al*^[62] described a new scoring system and reported that determining the amount of serum creatinine changes within 48 h was more capable than the RIFLE or AKIN criteria in predicting post-surgical outcomes.

This idea and the results of other studies encouraged researchers to propose a new definition. The KDIGO workgroup has recently reviewed these criteria and published a single definition for use in both clinical practice and research. AKI is defined when any of the following three criteria are met: an increase in serum creatinine by 50% in seven days, an increase in serum creatinine greater than 0.3 mg/dL in 48 h or oliguria^[1]. There is a paucity of data to judge KDIGO as few studies have employed this criterion to date^[63,64]. However, AKI incidence using KDIGO definition is probably lower than that using AKIN and RIFLE. Reported incidences of AKI in different studies ranged from 26%-49% for AKIN^[55,60], 19%-30% for RIFLE^[55,60] and 15%-16% for KDIGO^[63,64].

Thanks to the development of consensus systems for the definition of AKI, it is possible currently to compare studies around the world and newer definitions have improved their employment in cardiac patients. Nevertheless, we are still far from an ideal practical definition of CSA-AKI. One reason may be the effect of the minimal changes in creatinine on outcome. Although this has been investigated largely in patients undergoing cardiac surgery^[13,62], it is not limited to cardiac patients^[65]. The AKIN definition sets a lower minimum level of serum creatinine as the diagnosis cut off point for AKI. However, even people who are outside of the minimum level have a worse outcome compared to patients with almost no change in serum creatinine. As employing the current systems for AKI definition in clinical practice is not easy, many of the studies performed to date have utilized these definitions partially. This is probably more pronounced in the RIFLE criteria which require seven days of follow-up

for the diagnosis to be completed^[66].

AKI biomarkers, creatinine as a biomarker

Conventional biomarkers: An ideal biomarker for AKI is noninvasive, specific and sensitive for the detection of AKI within 24 h and is detected and measured in a rapid and reproducible way. Moreover, it should stratify risk and identify AKI subtypes^[1,27,67,68]. A single biomarker that can fulfill all these criteria has yet to emerge^[69]. Serum creatinine as a biomarker is still the only reliable tool for the assessment of AKI. Urine output is readily available and more sensitive to hemodynamic changes compared to creatinine. However, its variations are not specific, especially during cardiac surgery with cardiopulmonary bypass (CPB), and unavoidable hemodynamic changes, due to medications, such as diuretics, mannitol and other fluids, and possible measures such as ultrafiltration. In addition, the well-known term of non-oliguric renal failure denotes that normal urine output does not guarantee normal renal function^[70,71]. The other marker, urinalysis, can differentiate pre-renal from renal failure in patients with decreased urine output which is very helpful in guiding treatment. Obviously urinalysis is not suitable for prophylactic measures due to its delayed response to renal insult^[71].

With regard to eGFR formulas, we know that there is a lag between the renal event and serum creatinine changes that may be as long as 48 h, while we expect to know the occurrence of renal impairment immediately after surgery. As creatinine is not a sensitive measure, GFR may decrease up to 50% before the creatinine starts to change. Moreover, as creatinine is not specific, its value is influenced by changes in age, gender, race and muscle mass, as discussed before. In cardiac surgery, changes in total body volume, protein intake and medications may extend the list^[27,72]. These factors are so important that, for instance, volume overload was reported to be superior to creatinine in predicting outcome after cardiac surgery in a recent study^[73].

Novel biomarkers: Using the most sensitive and specific biomarker for AKI is the ideal solution for the optimal estimation of GFR and rapid diagnosis of renal insult. As was noted, such a biomarker should be biologically stable and as a laboratory assay should be quick, reliable and cost effective with a high discriminative power^[67]. So important is this issue that finding a suitable biomarker was recommended as the key search area in 2005^[74]. Currently, two large studies are underway to assess the role of novel biomarkers in the diagnosis and prognosis of AKI: multicenter National Heart, Lung and Blood Institute-sponsored Translational Research Investigating Biomarker Endpoints in AKI (TRIBE-AKI) study and the Assessment, Serial Evaluation and Subsequent Sequelae of AKI study. The latter is also aimed at evaluation of long term complications of AKI^[75]. The results of these large studies are expected to shed sufficient light on the matter.

In recent years, more than 20 biomarkers have been introduced and most of them have been tested in studies of post-cardiac surgery^[68,76]. Four novel biomarkers have been studied most frequently: neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1) as markers of tubular injury and cystatin C as a marker of glomerular function. NGAL, followed by IL-18, is more promising as an early diagnostic tool and may qualify for entry into clinical practice. KIM-1 has delayed response and cystatin C needs adjustment for age, gender and race^[2,69,77].

NGAL: NGAL is a protein that normally binds to small iron-carrying molecules. NGAL is significantly upregulated in response to renal tubular injury. Role of NGAL in the diagnosis of AKI has been the most extensively studied in cardiac surgery^[78]. First, animal studies in 2003 showed that NGAL was markedly upregulated early after ischemic injury^[79]. Then its rapid rise following renal insult drew attention. Level of urinary NGAL one hour post-CPB significantly predicted the risk of AKI after cardiac surgery^[80]. Plasma NGAL levels two hours after CPB were strongly correlated with the duration and severity of AKI^[81]. Other studies showed that NGAL levels were predictive of CSA-AKI when measured both in urine and plasma^[82-85].

It is noteworthy that the predictive power of NGAL in pediatric surgery is striking, whereas its sensitivity and specificity for AKI prediction in adult cardiac surgery is not high enough to employ it as the sole biomarker for CSA-AKI^[78,86]. It shows that the nature of CSA-AKI in adults is probably more complex. Degrees of chronic renal impairment before cardiac surgery may explain part of this inconsistency between the response of biomarkers to renal insult in adults and children. It is evident from recent studies that the diagnostic performance of NGAL is significantly influenced by baseline renal function^[84,87].

IL-18: IL-18, a pro-inflammatory cytokine, is a biomarker of AKI and is detectable in urine four to six hours after CPB, peaking at 12 h^[88]. A multi-center study showed that plasma NGAL and urine IL-18 peaking within 6 h after cardiac surgery not only predicted AKI earlier than serum creatinine, but also predicted important outcomes such as length of stay in the ICU and hospital, dialysis and death^[89].

However, there are some challenges regarding the use of the currently available biomarkers. First, biomarkers are being evaluated in comparison with creatinine as a gold standard while the weakness of serum creatinine to be a sensitive and specific marker has been the main cause of directing research into finding novel biomarkers^[90]. Second, many of the studies undertaken to date have excluded patients with CKD^[70] while CKD is the most important risk factor for postoperative AKI. Discrepancy between clinical practice and the results of research may arise as biomarkers are under the influence of baseline renal function^[11,12]. Third, the level of bio-

Table 2 Risk factors for acute kidney injury

Preoperative	Intraoperative
Patient related	Patient related
Renal dysfunction/high SCr¹	Low venous compliance
Advanced age	Low systemic vascular resistance
Female gender	Autoregulatory systems disturbances
NYHA FC IV	Low output syndrome
Reduced LVEF or CHF	(pressor/IABP need)
Left main CAD	Type of surgery
Diabetes mellitus	Valvular
Poor glycemic control	Re do surgery
Peripheral vascular disease	Emergency
COPD	
Coexisting liver disease	
Preoperative IABP	
Pulmonary rales	
Genetic predisposition	
Modifiable	Procedure related ³
Extremes of SBP ²	On-pump cardiac surgery
Sepsis ²	Nonpulsatile flow on CPB
Medications (NSAID, ARB)	Hypothermic CPB
Contrast dye	Deep hypothermic circulatory arrest
	Duration of CPB (> 100-120 min)
	Perfusion pressure
	Hemodilution during CPB
	Blood transfusion
	Hemolysis
	Embolism

¹Risk factors with higher level of evidence are in bold; ²both patient related and modifiable; ³and also modifiable. NYHA FC IV: New York Heart Association Function class IV; LVEF: Left ventricle ejection fraction; CHF: Congestive heart failure; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; IABP: Intra-aortic balloon pump; SBP: Systolic blood pressure; NSAID: Nonsteroidal anti-inflammatory drug; ARB: Angiotensin receptor blockers; CPB: Cardiopulmonary bypass; SCr: Serum creatinine.

markers increases in response to injury. Although novel biomarkers are superior due to earlier response, the ideal biomarker would be one that predicts AKI preoperatively. Promising results have been reported with ouabain^[91]. Fourth, the pathogenesis of AKI is multifactorial. Hemodynamic, inflammatory and nephrotoxic factors are responsible and overlap each other in leading to kidney injury^[25]. This complex pathology affects finding a unique biomarker with high accuracy in the diagnosis of AKI. Consequently, no biomarker by itself is an accurate and reliable predictor for the diagnosis and risk estimation in AKI. Combination of biomarkers as a diagnostic panel would probably allow the determination of the risk and severity, as well as the early diagnosis of AKI^[76,92].

RISK FACTORS FOR HIGH PERIOPERATIVE SERUM CREATININE

Risk factors for increased level of serum creatinine and the development of AKI have been widely studied^[10,71]. There are two main groups of risk factors: preoperative and intraoperative. Most of the preoperative risk factors are patient-related and most of the intraoperative risk factors are procedure-related. Usually, intraoperative risk

factors are more likely to be modifiable^[25] (Table 2). Post-operative factors, such as blood drainage and need for excessive transfusion and emergent exploration, as well as myocardial infarction, are of limited interest due to late onset and low chance of their benefit in AKI prediction and prevention^[10].

Preoperative risk factors

Preoperative risk factors are not the same in different studies. The most reported risk factors include advanced age, female gender, New York Heart Association Function class IV, reduced left ventricular ejection fraction or congestive heart failure, diabetes mellitus, poor glycemic control, peripheral vascular disease and chronic obstructive pulmonary disease. Other factors such as the need for preoperative intra-aortic balloon pump and pulmonary rales have been noted in studies. However, the most predictive risk factor has consistently been preoperative renal dysfunction^[2,71]. Thakar *et al*^[14] developed a risk index for predicting the need for dialysis after cardiac surgery based on preoperative factors. This study showed that the value of preoperative serum creatinine as an equivalent for renal dysfunction is the most important predictor for AKI.

Several studies have suggested that medications such as non-steroidal anti-inflammatory drugs and angiotensin receptor blockers (ARB) be stopped before cardiac surgery in order to decrease the risk of AKI^[25]. More recently, genetic predisposition to AKI has been studied. According to many polymorphism studies, apolipoprotein was associated with AKI and its epsilon-4 allele has been the only genotype protective against AKI compared to other forms of allele^[93,94].

Intraoperative risk factors

Contrary to many preoperative risk factors that are well known for their role in the development of CSA-AKI, the identification of intraoperative risk factors is challenging. Maintaining stable hemodynamics is probably the most important point in kidney protection during cardiac surgery, especially on the CPB. This is supported by the finding that many intraoperative risk factors are associated with hemodynamic instability: low-output syndrome; intraoperative intra-aortic balloon pump use; pressor need prior to CPB; and the need for deep hypothermic circulatory arrest. However, the management of hemodynamic changes is not easily feasible because patient factors such as venous compliance, systemic vascular resistance and autoregulatory systems are responsible for cardiovascular stability during cardiac surgery and are difficult to control^[10].

Rather than surgery type (valvular, re do, emergency), modifiable procedure-related risk factors include on-pump cardiac surgery, CPB nonpulsatile flow and hypothermic CPB. Current data is insufficient to confirm the association between these CPB parameters and the risk of CSA-AKI^[2,71]. Other more established CPB-related risk factors are duration of CPB (> 100-120 min), perfu-

sion pressure, hemodilution during CPB, blood transfusion, hemolysis, most commonly due to cardiotomy suction, and embolism^[2,95,96]. The role of CPB in inducing systemic inflammatory response syndrome (SIRS) and consequently CSA-AKI has been shown in different cardiac surgery events. The inflammation is related to perfusion pressure, hemodilution, blood transfusion, hypothermia, hemolysis and embolism^[97,98]. SIRS and other physiological untoward events explain how much longer CPB time increases the incidence of CSA-AKI. A meta-analysis in 2009 showed that mean CPB time and mean cross clamp time were significantly longer in patients who developed AKI. No safe time limit has been reported, however^[99].

Surgical technique

Surgical techniques with minimum CPB usage potentially lessen the adverse complications of the inflammatory response. Minimally invasive cardiac surgery, including transcatheter aortic valve implantation, or minimally invasive mitral valve surgery decreases the incidence of AKI^[100]. The other technique is mini CPB or miniaturized extracorporeal circuit with unproven efficacy in CSA-AKI prevention^[101]. Off-pump coronary artery bypass (OPCAB) is another technique to ameliorate CPB-related complications and aortic manipulations. However, it is interesting that the effectiveness of OPCAB in preventing CSA-AKI is controversial and still one of the most debated topics in cardiac surgery. Although OPCAB has been shown to be superior in many studies^[102-105], the results of recent large trials results have documented that it does not decrease important endpoints, especially the need for RRT^[106,107]. This may place an emphasis on the importance of hemodynamic stability in AKI prevention on account of the fact that during OPCAB, episodes of hypotension are inevitable. Overall, we conclude that at least in patients with lower risk for AKI, OPCAB may not decrease the likelihood of kidney impairment after cardiac surgery.

Hemodynamic

Perioperative hypotension during CPB increases the incidence of CSA-AKI. It is more important to preserve end-organ function and cellular oxygen delivery during CPB with its unique pressure and nonpulsatile flow characteristics. Thus, it is not the absolute hypotension but perfusion pressure that plays a pivotal role in protecting susceptible organs such as the kidney against CSA-AKI. The kidney medulla is more vulnerable since its oxygen delivery is already low^[108,109]. The difference between preoperative and intraoperative blood pressure may be a more important predictor of CSA-AKI compared to absolute hypotension. A study in 2010 showed that when this difference is more than 25 mmHg the incidence of CSA-AKI increases^[110].

Hemodilution

The carrying capacity of oxygen is influenced by hemo-

dilution which is inevitable during CPB. This adds to hemodynamic changes due to nonpulsatile flow and puts the kidney at danger of ischemia^[109]. It has been suggested that hematocrit levels less than 24% increase the risk of CSA-AKI^[111-113]. However, in all probability, preoperative hematocrit plays an important role^[114]. The most important factor is the balance between oxygen delivery and oxygen consumption which is crucial everywhere in the body, not least in the kidney which is more susceptible to ischemia^[124]. Even the probable risk of hypothermia during CPB may be explained by reperfusion ischemia due to rapid rewarming^[115].

That hemodilution has some adverse effects does not mean that blood transfusion is absolutely beneficial in improving renal function. RBC storage more than 14 d has been associated with increased organ injury^[116]. Moreover, the adverse effects of packed cell transfusion when hemoglobin level is not low outweigh its benefits^[117,118].

Evidence-based blood conservation techniques include increasing preoperative blood volume by drugs such as erythropoietin and decreasing postoperative blood loss (tranexamic acid and aminocaproic acid), preserving the patient's own blood by autologous techniques, such as predonation and intraoperative hemodilution, and intraoperative cell salvage^[119].

CPB flow

Pulsatile flow is believed to improve renal function by decreasing peripheral vascular resistance, optimizing microcirculation and decreasing tissue edema^[120,121]. However, the inconsistent results of studies cannot support its routine use for protection against CSA-AKI^[122-124].

RISK MODELS FOR AKI AFTER CARDIAC SURGERY

Identification and categorization of high-risk patients allows optimal decision-making for earlier intervention and better management, along with the identification of the patients who do not respond to conventional treatments. Risk prediction models can also be used as research tools to select high risk patients for performing studies on AKI. Several risk stratification models have been developed by research groups in patients undergoing different surgeries^[11,125].

As discussed before, CSA-AKI has its own characteristics. Although some risk factors for AKI are common in general and cardiac surgery, the risk scores developed in a general surgery population underestimate the risk of AKI in cardiac surgery^[126]. There are several risk prediction models that have been developed in the field of cardiac surgery^[11,14,15,127-130].

Chertow *et al*^[11] developed the first risk score using a large population database in 1997. This algorithm stratified preoperative risk for dialysis based on data from 43 medical centers gathered in the Continuous Improvement in Cardiac Surgery Study. Then three other predictive risk models were developed, all of which aimed at predicting

the need for dialysis as outcome^[14,127,128]. The most validated model with a high level of precision and the best discriminative power is the Cleveland Clinic Score which was published in 2005 by Thaker *et al*^[14] (Candela-Toha *et al*^[126], Di Bella *et al*^[131], Englberger *et al*^[132] and Heise *et al*^[133]).

In 2006, the Society of Thoracic Surgeons Bedside Risk Tool was developed by Mehta *et al*^[128] through the analysis of a multicenter dataset of more than 600 hospitals. Simplified Renal Index was developed by Wijesundera *et al*^[127] from a Toronto cohort in 2007. Validation studies by other researchers indicate that recalibration of every risk score is needed for optimal risk prediction in any center^[134-136]. Other available models are aimed at predicting AKI not requiring dialysis. They have not been externally validated, however, and due to different definitions of AKI it is difficult to generalize them^[16,129,130].

The most important criticism to the available risk models is their lack of prediction for CSA-AKI. There are still different definitions for AKI and there is no guideline to recommend a specific prediction model^[2,48]. As discussed before, we need to add novel biomarkers to the current risk models and AKI definitions so as to be able to develop scoring systems for the prediction of the earlier stages of AKI. A study by Parikh *et al*^[89] indicated that adding urine IL-18 and plasma NGAL to the risk models improved risk prediction by 25% and 18% respectively.

CREATININE AND THE OUTCOME PREDICTION IN CARDIAC SURGERY

The critical role of creatinine as a strong predictor has been incorporated in the different mortality risk scores that are currently in use for cardiac surgery patients^[3,49,137]. Known risk models have employed a wide range of risk factors from only three to dozens^[3,4]. However, high level of serum creatinine or its equivalents (past history of kidney dysfunction, need for renal replacement therapy and/or dialysis) has been the constituent in almost all of them. The first scoring system was developed by Parsonnet *et al*^[138] in 1989, which included serum creatinine in 14 independent variables. Subsequently, Higgins *et al*^[139] proposed the Cleveland Clinic score in 1992. Cleveland Clinic score was basically developed for coronary artery bypass graft (CABG) operations with or without associated valve surgery and included creatinine among 9 independent variables included in this score. Another mortality predictor introduced in 1992 was the Northern New England score which was developed for isolated CABG operations and included preoperative dialysis dependency as a surrogate for high serum level of creatinine^[140]. Nilsson *et al*^[3] and Magovern *et al*^[141] developed another risk algorithm to be applied in isolated CABG with promising results compared to a group of 18 risk models.

In the last decade, the additive^[142] and the logistic^[143] EuroSCORE predicting tools were developed and subsequently widely validated. These scores are prepared to be applied in all cardiac surgeries in adult patients and

each of them includes 17 independent variables. Serum creatinine receives a score of two when its absolute value is more than 200 $\mu\text{mol/L}$ (2.25 mg/dL). EuroSCORE overestimates mortality and its performance in high risk patients is not good. EuroSCORE II was released in 2012 to improve the accuracy of this measure^[144].

The risk score developed by the Society of Thoracic Surgeons is more complex, built on a database with more than five million records and including several hundred variables^[145]. The risk calculator is available freely at: <http://riskcalc.sts.org/STSWebRiskCalc273/>. On the other hand, Ranucci *et al*^[4] recently proposed a simple score with only three variables, including creatinine, and demonstrated that this risk model was superior to or as effective as the other more complex risk scoring systems. Creatinine in this score has an absolute cut off point of 2 mg/dL. In patients with serum level of creatinine higher than 2 mg/dL, one point is added to sum of the patient's risk. The formula is as follows: age (years)/ejection fraction (%) + 1 (if serum creatinine > 2 mg/dL).

The main weakness of existing risk models is their inaccuracy in different time periods and patients' conditions and various regional settings which emphasizes the dynamic trends in cardiac surgery^[146,147]. Moreover, known risk models are principally prepared to predict mortality. So, we probably are unable to accurately predict morbidity and cost of care by the available risk models. The other major flaw is the lack of a consensus definition of time span for mortality by these models^[137].

PREVENTION AND TREATMENT ON THE HORIZON

Briefly, no treatment or prophylactic measure studied thus far has received sufficient evidence-based support to be employed in AKI management^[66]. However, avoidance of AKI by preventive measures remains the mainstay of management in high risk patients. Contrast induced AKI is probably an exception in that it is preventable and manageable by hydration, N-acetyl cysteine and bicarbonate^[148].

Renoprotective measures include preventive simple maneuvers such as avoidance of nephrotoxic drugs, hydration, glycemic control, maintenance of renal perfusion and goal directed therapy (GDT), as well as more advanced pharmacological interventions^[1,2,70,71] (Table 3).

Preventive measures

Renal injury can be mitigated by two approaches: preventing CSA-AKI from being superimposed on CKD by appropriate risk assessment and preventing subclinical or silent AKI from occurring before cardiac surgery. Management of the adverse effects of contrast dye is an example of the second approach. The role of contrast dye in the occurrence of CSA-AKI is well known and as it is not avoidable, the minimum possible dose of preferably newer non-ionic contrast with lower osmolality should be used^[149,150]. Timing of surgery following contrast angiography may play a role in CSA-AKI. It has been shown

Table 3 Potential preventive measures and pharmacological interventions in acute kidney injury

Preventive measures
Avoidance of nephrotoxic drugs
Angiotensin-converting enzyme inhibitors
Angiotensin receptor blockers
Hydration
Glycemic control
Maintenance of renal perfusion
Goal directed therapy
Ischemic preconditioning
Prevention of CI-AKI
Hydration
N-acetyl cysteine
Bicarbonate
Timing of surgery
Pharmacological interventions
Fenoldopam
Nesiritide
Sodium bicarbonate
Mannitol
Atrial natriuretic peptide
Brain-type natriuretic peptide
Early postoperative renal replacement therapy
Continuous renal replacement therapy
Ultrafiltration

CI-AKI: Contrast induced acute kidney injury.

that cardiac surgery within 24 h of angiography is not safe. In the case of large contrast dose administration it is better to postpone surgery for five days^[151,152].

Sufficient hydration is protective not only in patients at risk of contrast-induced nephropathy^[153], but also in patients with underlying renal insufficiency^[154]. Ideal fluids have been thoroughly investigated to be recognized, without consistent results^[1,71]. It appears from studies to date that colloids are not superior to crystalloids in improving outcome^[155,156]. Moreover, recent studies have shown that contrary to previous belief, clinical application of semisynthetic colloids, especially hydroxyethyl starch solutions, are increasingly difficult to justify in the perioperative period^[156]. Of more importance is probably maintaining normal renal perfusion as 80% of patients diagnosed with AKI after surgery have had an episode of perioperative hemodynamic instability^[157]. GDT, involving the use of enough fluid and blood along with inotropes to optimize hemodynamic parameters and oxygen delivery, is a recommended strategy^[156,158,159]. Fluids are required to be prescribed as a drug^[156]. This is possible through the employment of physiological parameters such as the plethysmographic variability index, stroke volume variation and pulse pressure variation in advanced monitoring systems^[159]. Further studies are needed to optimize protocols^[156,159].

Angiotensin-converting enzyme inhibitors and ARB are potential nephrotoxic medications commonly used in cardiac patients. Avoiding them has not been shown to change the incidence of CSA-AKI and the subject is still controversial^[160,161].

Other measures, such as ischemic preconditioning us-

ing three 5 min intervals of ischemia separated by exactly the same times and interval of reperfusion in the thigh, have been shown to reduce the risk of CSA-AKI^[162].

Pharmacological interventions

Finding a pharmacological agent for the management of CSA-AKI has been challenging due to the absence of standard definitions and end-points^[1,2,26,70,163]. Many drugs have been investigated to date to control the serum level of creatinine and renal protection. Fenoldopam, a selective agonist of dopamine-1 receptor, is the only drug that consistently and significantly has reduced the risk of AKI, followed by nesiritide with initial promising results^[1,164,165].

Sodium bicarbonate was found in a known pilot study in 2009 to decrease the risk of AKI by 20%^[166]. However, another large study in 2012 questioned its usefulness^[167]. This is also true for statins. First reports on its usefulness were not supported by the following studies^[168-171].

It has been known since 2001 that low-dose dopamine is not justified for the prevention and treatment of AKI^[172,173]. Furosemide infusion, especially in combination with dopamine, is even detrimental and may increase postoperative creatinine^[174,175]. Mannitol is an osmotic diuretic that has been used routinely in priming solution for decades. Currently there is debate on its usefulness in cardiac surgery and studies have been inconclusive. However, it is probably reasonable to continue its use as a harmless fluid until strong evidence, guidelines and recommendations are published^[176,177].

Atrial natriuretic peptide and brain-type natriuretic peptide (BNP) are endogenous diuretics with promising effects on renal function in cardiac surgery^[178-180]. BNP is highly associated with postoperative AKI such that it has been considered as a biomarker for AKI in the recent report of TRIBE-AKI study^[181]. Nesiritide, the recombinant human BNP, has been shown to be beneficial according to initial results. Further studies are required before applying nesiritide routinely in daily clinical practice^[182,183].

N-Acetylcysteine has protective effects on contrast-induced nephropathy^[184]. Be that as it may, its prophylactic administration in cardiac surgery is under question. Recent meta-analyses have concluded that current data do not support its routine use in cardiac surgery and it has obtained least strength evidence among prophylactic measures for renal protection^[1,163,185].

Current data is insufficient to support preoperative prophylactic RRT. The best starting time for postoperative RRT is also controversial. Most studies have found lower mortality with the earlier initiation of RRT^[163,186,187]. In addition, recent guidelines suggest that using continuous RRT is superior to standard intermittent RRT in hemodynamically unstable patients^[148]. It is clinically indicated and applicable, although reviews to date have not found differences in survival between the two modes^[188]. Similarly, the benefits of ultrafiltration on CSA-AKI prevalence and severity in adult cardiac surgery warrants further investigation.

CONCLUSION

Recent advances in diagnosis and management of CSA-AKI have opened new perspectives for scientists and medical practitioners. However, creatinine still plays the main role in diagnosis and prediction. New consensus classification for AKI (KDIGO) and new formula for eGFR calculation (CKD-EPI) are promising for better evaluation of patients at risk of postoperative AKI. Incorporating a panel of novel biomarkers in diagnosis and prevention could enhance the quality of the prediction and cause supportive care to be employed earlier. Results of large studies are expected to qualify the capability of these achievements to improve patients' daily care. With respect to the AKI prevention and management, notwithstanding the large number of studies, more attempts are required to reach the optimal prophylactic and therapeutic goals.

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Newer methods of cardiac output monitoring

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Abstract

Cardiac output (CO) is the volume of blood ejected by each ventricle per minute and is the product of stroke volume and heart rate. CO can thus be manipulated by alteration in heart rate or rhythm, preload, contractility and afterload. Moreover it gives important information about tissue perfusion and oxygen delivery. CO can be measured by various methods and thermodilution method using pulmonary artery catheter (PAC) is till date considered as gold standard method. Complications associated with PAC led to development of newer methods which are minimally or non-invasive. Newer methods fulfil other properties like continuous and reproducible reading, cost effective, reliable during various physiological states and have fast response time. These methods are validated against the gold standard with good level agreement. In this review we have discussed various newer methods of CO monitoring and their effectiveness in clinical use.

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Key words: Cardiac output; Pulse contour analysis; Pulse power analysis; Bioimpedance; Doppler; Echocardiography

Core tip: This is review of newer methods of cardiac output monitoring which are minimally invasive and

have lesser complications as compared to gold standard methods.

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INTRODUCTION

Cardiac output (CO) monitoring is an important tool in high risk critically ill surgical patients in whom large fluid shifts are expected along with bleeding and hemodynamic instability. It is an important component of goal directed therapy (GDT), *i.e.*, when a monitor is used in conjunction with administration of fluids and vasopressors to achieve set therapeutic endpoints thereby improving patient care and outcome. CO cannot be measured reliably by clinical examination and routine assessment. There are various methods of CO monitoring based on Ficks principle, thermodilution, Doppler, pulse contour analysis and bioimpedance. Each method has its own merits and demerits (Table 1). An ideal CO monitor should be minimally or non-invasive, continuous, cost effective, reproducible, reliable during various physiological states and have fast response time^[1]. Advances in the computer software and hardware have led to development of newer methods of CO monitoring with minimal or no vascular access.

Methods of CO monitoring are broadly classified as follows: (1) Invasive-Intermittent bolus pulmonary artery thermodilution, Continuous pulmonary artery thermodilution; (2) Minimally invasive-Lithium dilution CO (LiD-CO), Pulse contour analysis CO (PiCCO and FloTrac), Esophageal Doppler (ED), transesophageal echocardiography (TEE); and (3) Non-invasive-Partial gas rebreathing, Thoracic bioimpedance and bioreactance, endotracheal cardiac output monitor (ECOM), Doppler method and Photoelectric plethysmography.

Table 1 Advantages and disadvantages of methods of cardiac output monitoring

No	Device	Type	Advantages	Disadvantages
1	PAC	Invasive	Gold standard	Catheter related complications
2	Continuous CO by PAC	Invasive	Continuous CO measurement	Catheter related complications
3	LiDCO	Minimally invasive	Only one arterial line	Cost
			Continuous CO measurements	Requires good arterial waveform
			Measure SV and SVV	Requires Calibration
4	PiCCO	Minimally invasive	Continuous CO measurement	Contraindicated in Lithium therapy
			Effective during hemodynamic instability	Requires good arterial waveform
5	FloTrac	Minimally invasive	Continuous CO measurement	Requires calibration
			No calibration	Requires good arterial waveform
6	PRAM	Minimally invasive	No calibration	Still not validated
7	ED	Minimally invasive	Simple to use	Measure flow only in descending thoracic aorta
			Reliable	Assumptions about aortic size may not be accurate
			Useful in GDT	
8	TEE	Minimally invasive	Evaluate cardiac anatomy preload and ventricular function	Cost
			Ease of use	Skilled personnel
9	Partial non-rebreathing systems	Non invasive	Continuous CO measurement	Affected by changes in dead space or V/Q matching
10	Thoracic bioimpedance	Non invasive	Continuous CO measurement	Affected by electrical noise, movement, temperature and humidity
				Requires hemodynamic stability
				Not useful in dysrhythmias
11	ECOM	Non invasive	Continuous CO measurement	Coronary blood flow not recorded
				Electrocautery produces interference

CO: Cardiac output; LiDCO: Lithium dilution CO; PiCCO and FloTrac: Pulse contour analysis; PRAM: Pressure recording analytic method; ED: Esophageal Doppler; TEE: Transesophageal echocardiography; ECOM: Endotracheal cardiac output monitor; PAC: Pulmonary artery catheter; SV: Stroke volume; SVV: SV variation; GDT: Goal directed therapy.

INVASIVE METHODS

Cardiac output measurement by pulmonary artery catheter

Pulmonary artery catheter (PAC) as a monitor to measure flow and pressure was developed by Dexter^[2] and modified later on by Swan *et al*^[3] to measure CO and central filling pressures. It is still considered as gold standard monitor to measure CO since 1970's^[4]. It has been used as a monitoring tool in high risk surgeries and critical care units.

However, its use has been associated with various complications like pneumothorax, arrhythmia, infection, pulmonary artery rupture, valve injury, knotting and thrombosis leading to embolism^[5,6]. Also, various technical errors may lead to false readings like loss of injectate, variability of temperature, thermistor malfunction, clot over catheter tip, coiling of catheter or timing of injectate > 4 s. Moreover, intracardiac shunts, mechanical ventilation or valvular dysfunction may lead to incorrect readings. These errors and adverse effects led to the development of less invasive methods of CO monitoring^[7,8]. Thus the main objective of present review article is to focus on the newer methods of CO monitoring that are validated with the gold standard method and have ease of use and lesser complications.

CONTINUOUS CO MEASUREMENT BY PAC

Continuous CO (CCO, Edwards Lifesciences, Irvine,

California, United States) is a modification of PAC with copper filament in the catheter that remains in the right ventricle. There is intermittent heating of blood in the right heart by the filament and the resultant signal is captured by thermistor near the tip of the catheter. Average value of CO measured over time is displayed on the monitor. Main advantages of CCO over conventional PAC are avoidance of repeated boluses thus reducing the infection risk and operator errors^[5]. Moreover, continuous monitoring of stroke volume (SV), systemic vascular resistance (SVR) and mixed venous saturation can also be performed with this catheter. We found CCO to be comparable to conventional intermittent thermodilution CO in patients undergoing off pump coronary artery bypass grafting surgery (OPCAB) at various time points^[9].

Literature review regarding use of PAC in operating room and intensive care units (ICU) revealed both benefits and risks. Gore *et al*^[10] showed that PAC use increased mortality after myocardial infarction and SUPPORT trial also showed increased mortality at 30 d^[11]. Complications have led some authors to call for complete moratorium on PAC use^[12]. Various randomized controlled trials (RCT) also demonstrated increased incidence of adverse events in comparison to central venous pressure 1.5% *vs* 0.7% with no significant difference in mortality and length of stay in hospital^[13]. Later on PAC-MAN trial failed to show any benefit or harm with the use of PAC^[14]. Its use in patients undergoing OPCAB also showed no difference in mortality and final outcome^[15]. ESCAPE trial demonstrated functional improvement with PAC guided

therapy used in patients with congestive heart failure^[16].

In spite of various arguments PAC is still considered as the “Gold Standard” for monitoring of CO. However, due to inherent risk associated with its use investigators are trying to develop a minimally or non-invasive monitor for CO which has all the characteristics of an ideal monitor. Various methods based on arterial pulse contour analysis, plethysmography, Fick’s principle or bioimpedance have been developed. Its values should be within limits of agreement (Bland Altman analysis)^[17] of the “gold standard”. We will discuss these methods in the present review.

MINIMALLY INVASIVE METHODS

Pulse power analysis

This method is based on the principle that change of the blood pressure about the mean is directly related to the SV. Various factors affect its accuracy like compliance of the arterial tree, wave reflection, damping of the transducer and aortic systolic outflow^[18].

LiDCO (Cambridge, United Kingdom) system combines pulse contour analysis with lithium indicator dilution for continuous monitoring of SV and SV variation (SVV). Root mean square method is applied to the arterial pressure signal and called “nominal SV” and using a patient specific calibration factor is further scaled to an “actual SV”^[19]. It is a minimally invasive technique first described in 1993^[18] and requires a venous (central or peripheral) line and an arterial catheter. A bolus of lithium chloride is injected into venous line and arterial concentration is measured by withdrawing blood across disposable lithium sensitive sensor containing an ionophore selectively permeable to Li. CO is calculated based on Li dose and area according to the concentration time circulation^[20].

It requires calibration every 8 h and during major hemodynamic changes. It is contraindicated in patients on Li therapy and calibration is also affected by neuromuscular blockers as quaternary ammonium residue causes electrode to drift^[20]. Its accuracy is affected by aortic regurgitation, intraaortic balloon pump (IABP), damped arterial line, post-aortic surgery, arrhythmia and intra or extracardiac shunts^[5,20].

This device has been studied in relation with PAC. Linton *et al*^[18] found good correlation with PAC. Good correlation with PAC has also been found in patients undergoing liver transplantation^[21]. Pearse *et al*^[22] studied it for early goal directed therapy and revealed fewer complications and shorter length of hospital stay.

Pulse contour analysis

It is based on the principle that area under the systolic part of the arterial pressure waveform is proportional to the SV^[23]. It was first described by Erlanger and Hooker in 1904 and suggested that CO was proportional to arterial pulse pressure^[24]. In this method the area is measured post diastole to end of ejection phase divided by aortic

impedance that measures SV. It also measures SVV and pulse pressure variation (PPV) which is useful in predicting fluid responsiveness. SVV is the difference between maximum and minimum SV over the respiratory cycle and is caused by changes in preload with alteration in intrathoracic pressure. In addition to that shape of the arterial waveform (dP/dt), arterial compliance, SVR and patient specific calibration factors are also required for calibration^[24]. In 1970’s first algorithm was developed to continuously analyse the pressure waveform from arterial line^[25].

PiCCO system: The PiCCO system (PULSION medical system, Munich, Germany) was the first pulse contour device introduced and was replaced with PiCCO2 in 2007^[26]. It requires both central venous (femoral or internal jugular) and arterial cannulation (femoral/radial). Indicator solution injected *via* central venous cannula and blood temperature changes are detected by a thermistor tip catheter placed in the artery. Thus, it combines pulse contour analysis with the transpulmonary thermodilution CO to determine hemodynamic variables. It requires manual calibration every 8 h and hourly during hemodynamic instability^[27].

In addition, thermodilution curve can be used to measure intrathoracic blood volume (ITBV), global end diastolic volume (GEDV) and extravascular lung water (EVLW). GEDV and ITBV are a measure of cardiac preload and EVLW (interstitial, intracellular or intra alveolar) is a mean to quantify pulmonary edema. It also measures SVV/PPV which is marker of fluid responsiveness^[28].

PiCCO is a relatively invasive method as it requires both arterial and venous cannulation. Its accuracy may be affected by vascular compliance, aortic impedance and peripheral arterial resistance. Moreover, air bubble, clots and inadequate indicator may also affect the accuracy. Valvular regurgitation, aortic aneurysm, significant arrhythmia and rapidly changing temperature may also affect its accuracy^[29].

Various validation studies have found good correlation with PAC during coronary artery bypass grafting^[30]. However, that is not the case in patients undergoing OPCAB^[31]. In non-cardiac and critically ill patients good correlation has been observed^[32]. Significant errors have been reported during hemodynamic instability requiring recalibration^[33].

FloTrac system: FloTrac (Edwards LifeSciences, Irvine, United States) is a pulse contour device introduced in 2005 and is a minimally invasive method as it requires only an arterial line (femoral or radial). The system does not need any external calibration, is operator independent and easy to use. It is based on the principle that there is a linear relationship between the pulse pressure and SV^[19,34].

The algorithm used in this system uses SD of 2000 arterial waveform points which is calculated by arterial pressure waveform sampled each 20 s at 100 Hz. It in-

incorporates characteristics of the arterial waveform with patient specific demographics. The SV is estimated by following equation:

$$SV = SD_{AP} \times \mu$$

SD_{AP} = Standard deviation of data points that reflects pulse pressure.

μ = Conversion factor depends on arterial compliance, mean arterial pressure, waveform characteristics.

Vascular compliance is patient's biometric values (sex, age, height and sex)^[35] and waveform characteristics assessed by skewness (degree of asymmetry) and kurtosis (degree of peakedness) of the individual arterial pressure waveform. A change in vascular tone is represented by skewness and kurtosis. The conversion factor μ enables calculation of SV without external calibration. Second generation devices also developed that calibrate every minute leading to improved CO measurement^[36]. A third generation device with Dynamo tone technology that has automatic adjustment for change in the vascular tone has also been made^[37]. Good arterial waveform quality is a prerequisite for accurate reading of CO. Accuracy is affected in patients with significant arrhythmias, IABP or morbid obesity^[38].

Various studies have validated the efficacy of FloTrac with PAC and find good correlation. We have studied FloTrac with PAC in patients undergoing OPCAB and found good agreement. The mean bias and limits of agreement (2 standard deviations) expressed in liters per minute at respective points of measurement were -0.54 ± 1.12 , -0.37 ± 1.0 , -0.42 ± 1.50 , -0.25 ± 1.18 , -0.31 ± 1.28 , 0.41 ± 1.0 , 0.06 ± 1.50 , and 0.09 ± 1.40 ^[39]. However, in patients with low SVR undergoing liver transplantation or septicemia it is not found as accurate as PAC^[40-42]. It is found to be useful in patients undergoing major abdominal surgery who received GDT^[43]. Moreover, the site of the arterial cannulation is also an important determinant of accuracy. In severe vasoconstriction radial artery reading will underestimate the CO while in volume responsive patient volume redistribution to cerebral circulation will also impair the pulse contour analysis through radial artery^[3].

Pressure recording analytic method: Pressure recording analytic method (PRAM)-MostCare (Vytech, Padova, Italy) measures the area under the curve of arterial waveform. Major advantage is that it does not require external calibration and internal calibration is done by morphology of the arterial waveform. PRAM technology analyses whole cardiac cycle and area under the pressure wave (P/t) is determined^[44]. The P/t is divided into diastolic and systolic phase with 2 impedances based on different characteristics. However the accuracy of this method is still not proven.

EV1000/Volume view: A new calibrated pulse wave analysis method (VolumeView™/EV1000™, Edwards Lifesciences, Irvine, CA, United States) has been developed. It is based on pulse pressure analysis, which is calibrated by transpulmonarythermodilution and is currently

under trial. Its comparison with PICCO2 system in critically ill patients found comparable results^[45]. However; very few studies are available for its validation. We have just finished a study on its use for GDT in OPCAB and found it to be very useful.

Esophageal doppler

Esophageal Doppler uses a flexible probe with transducer at the tip. It is of the size of anorogastric tube and can be placed for longer period in intubated patients. At the midthoracic level it measures flow as it is presumed to be parallel to the descending aorta. Since aorta is considered as a cylinder, the flow can be measured by multiplying cross-sectional area (CSA) and velocity. Doppler ultrasound is used to measure the SV. Once an optimal flow profile has been obtained, the blood flow velocity is determined from the shift in frequency of red blood cells. This is done by the ultrasound processor using the Doppler equation:

$$V = f_d \times c / 2 \times f_0 \times \cos\theta$$

V = velocity of blood, f_d = Doppler shift in frequency, c = speed of ultrasound in tissue (1540 m/s), f_0 = initial ultrasound frequency, and θ = the angle of ultrasound beam in relation to the blood flow.

The velocity-time integral (VTI) is calculated from the area under the velocity-time curve and used as the stroke distance. The area can be calculated by nomogram or direct measurement. Thus SV is calculated as $CSA \times VTI$ and CO is calculated as $SV \times HR$ ^[24]. FTc i.e., corrected time flow can also be determined which is used as measure of cardiac preload^[46].

Major limiting factor is that it measures flow only in descending thoracic aorta which is 70% of total flow. A correction factor needs to be added to compensate aortic arch flow. Moreover discrepancies in flow may be seen in aortic coarctation, aneurysm or crossclamp, IABP and various metabolic states. Various factors like changes in pulse pressure, vascular compliance, volume status or inotropes may affect the CSA. In circulatory failure, it has been shown that CSA should be measured directly to prevent any inaccuracy in readings. Unchanged CSA may lead to underestimation of CO^[24]. Accurate velocity can only be determined by proper positioning of the probe which must be within 20° of the axial flow.

Various studies have compared ED with PAC and found good agreement with low bias. A meta analysis revealed it as a reliable method with low bias with limited efficacy^[47]. ED has also been used in GDT and shown greater improvement in SV and CO with faster recovery and shorter length of stay^[48]. In cardiac surgery, decreased hospital and ICU stay with decreased incidence of gut mucosal perfusion, without major complications has been shown with ED^[49]. We also studied this device in patients undergoing OPCAB and found that in comparison with PAC it cannot be used as a sole method for CO monitoring^[50].

TEE

TEE has now been a widely used monitor in periopera-

tive setting. It is an important tool for the assessment of cardiac structures, filling status and cardiac contractility^[51]. Moreover, aortic pathology can also be detected by TEE. Doppler technique is used to measure CO by Simpson's rule measuring SV multiplied by HR. Flow is measured by area under the Doppler velocity waveform that gives VTI and CSA is calculated by planimetry. Measurement can be done at the level of pulmonary artery, mitral or aortic valve. TEE views used for measurement are mid-esophageal aortic long axis view and deep transgastric long axis view with pulsed and continuous wave Doppler respectively. The ultrasound beam is parallel to the blood flow in transgastric view.

TEE has been validated with PAC with good limits of agreement^[52]. It is a useful tool in hemodynamically unstable patient under mechanical ventilation^[53]. However, a skilled operator is required, limited availability and cost factor are major limitations for its use. Standard TEE probe cannot be kept in the patient for too long. Hemodynamic TEE is a disposable thinner TEE probe which can be left *in situ* for several days.

NON INVASIVE METHODS

Partial gas rebreathing

It is also known as the NICO system (Novamatrix Medical Systems, Wallingford, Conn, United States) or partial gas re-breathing monitor and uses indirect Fick's principle to calculate CO. It is used in intubated patients under mechanical ventilation. At steady state, the amount of CO₂ entering the lungs *via* the pulmonary artery is proportional to the CO and equals the amount exiting the lungs *via* expiration and pulmonary veins.

During 30 s of re-breathing, the amount entering does not change, but the amount eliminated by expiration decreases and endtidal CO₂ increases in proportion to the CO^[24]. CO is calculated according to following formula:

$$CO = VCO_2 / C_vCO_2 - CaCO_2$$

Here VCO₂ is CO₂ consumption, CaCO₂ and C_vCO₂ is arterial and venous CO₂ content respectively. The diffusion rate of carbon dioxide is 22 times more rapid than that of oxygen, it is assumed that no difference in venous CO₂ (C_vCO₂) will occur, whether under normal or rebreathing conditions. A disposable circuit is connected to the ventilator circuit along with infrared CO₂ sensor, pneumotachometer and a rebreathing valve. Partial rebreathing is initiated every three minutes by opening the valve and pulmonary blood flow is calculated by difference between normal and rebreathing ratio^[54].

Major limitation is that tracheal intubation with fixed ventilator setting is required. It is also not very accurate in patients with severe chest trauma, significant intrapulmonary shunt, high CO states and low minute ventilation^[24]. Validation studies have not found accuracy of this device with PAC. Studies have shown underestimation preoperatively and overestimation postoperatively after cardiac surgery^[55]. Thus it has limited clinical applicability in comparison to PAC.

Thoracic bioimpedance

Thoracic bioimpedance (TEB) is a non-invasive method of CO monitoring. Initially it was used by astronauts in 1960s^[56]. It is based on the hypothesis by considering thorax as a cylinder perfused with fluid with specific resistivity. It measures the electrical resistance of the thorax to a high frequency, low amplitude current^[24].

Electrodes six in number are placed (two on either side of neck and four in lower thorax) on the patient and the resistance to current flowing from the outermost to innermost electrodes is measured. The bioimpedance is indirectly proportional to the content of thoracic fluid. Tissue fluid volume, pulmonary and venous blood, and the aortic blood volume all contribute to the TEB measurement. Changes in CO will change the amount of aortic blood and will be reflected in a change TEB^[5]. SV is calculated using the formula^[24]:

$$SV = VEPT \times VET \times EPCI$$

VEPT = volume of electrically participating tissue (gender, height, and weight).

VET = ventricular ejection time taken from the R-R interval.

EPCI = ejection phase contractility index which is indirectly proportional to TEB.

Major limitations like interference with electrocautery, proper electrode placement, patient's movements and arrhythmia may affect its accuracy. Studies in cardiac surgical patients revealed good correlation intraoperatively with a mean bias of -0.28 L/min. Presence of sternal wires, or arrhythmia may lead to inaccurate readings in the postoperative period^[57]. Results were also not encouraging in critically ill patients. Moreover, it has been considered as trend analysis monitor rather than a diagnostic one^[58].

Thoracic bioreactance

Thoracic bioreactance (NICOM device, Cheetah medical, Portland, Oregon) is a modification of TEB which avoids interferences by noise and external sources. It analyses changes in the phase of electrical voltage signal to the current applied across the thorax. Changes in electrical capacitive and inductive properties occurs secondary to change in intrathoracic volume.

The method involves placement of two dual electrodes on either side of the thorax. Sine-wave high-frequency (75 kHz) current is transmitted into the body through one electrode and other electrode is used by the voltage input amplifier. The mean of two will give final value^[59].

Electrocautery also affects its accuracy however if the device receives signal for atleast 20 s over a minute the CO value can be determined. Major advantage is the ease of use in intubated patients, arrhythmias, emergency room (ER), ICU and operating room (OR). Validating studies with PAC showed good correlation between the two methods with minimal bias^[57]. Moreover comparison with pulse contour devices like PiCCO and ED also showed comparable results^[58,60].

ECOM

ECOM (Con-Med, Irvine, Calif, United States) measures CO using impedance plethysmography. It is based on the principle of bioimpedance and current is passed through electrodes attached to endotracheal tube shaft and cuff. Current is passed from electrode on the shaft of endotracheal tube (ETT) and change in impedance secondary to aortic blood flow is detected by electrode on the cuff of ETT. An algorithm calculates SV based on impedance changes and CO can be calculated. Impedance is affected by aortic blood flow^[61].

Electrocautery affects its accuracy and coronary blood flow is not calculated. Moreover the technology is still adequately not validated in humans, is costly and has not become very popular.

Portable doppler device

Ultrasonic Cardiac Output Monitors (USCOM, Sydney, Australia) is a portable device which is non-invasive and uses a probe placed suprasternally to measure flow through the aorta or on the left chest to measure transpulmonary flow^[62]. It uses the Doppler principle as used with ED and TEE. Main advantage is the portability of the device and it can be used with ease in ER, OR, ICU and even in wards. Since it is a non-invasive device it can be used by trained nursing staff and is an important screening tool for postoperative cardiac surgical patients as well.

Major limitations are probe positioning as misalignment of ultrasound beam with blood flow may lead to errors and estimation of proper CSA in various physiological states is also important^[24].

We have used USCOM device in post cardiac surgical patients for both left and right sided CO, CI and SV measurements and found good agreement with PAC. On comparing the right-sided CO, SV, and CI with those of PAC, the mean bias was 0.03 L/min, 1.6 mL, and 0.02 L/min per square meters, respectively. The comparison of left-sided CO, SV, and CI with those of thermodilution revealed a means bias of 0.14 L/min, 1.0 mL, and 0.08 L/min per square meters, respectively^[63]. We further studied this device in OPCAB and found good correlation with PAC. The CO had a mean bias of -0.13 L/min and limits of agreement (mean bias \pm 2SD) at -0.86 and 0.59 L/min^[64].

Photoelectric plethysmography

The Nexfin HD (BMEYE B.V, Amsterdam, Netherlands) is a completely non-invasive pulse pressure analysis device that assesses pulse pressure using photoelectric plethysmography in combination with a volume-clamp technique (inflatable finger cuff). CO is derived by Modelflow method. There are very few validation studies to state its efficacy^[65].

CONCLUSION

There are various newer devices for CO monitoring available in clinical practice that are validated against the

gold standard method. Newer devices have the advantage of being minimally or non-invasive and portable. Hence, a few of them can be used outside the OR and ICU. Validation with PAC and other limitations may still be an obstacle for their use in different clinical scenarios. The criteria for selection of newer devices should be based on the institutional protocol and clinical condition of the patients. More RCT's are needed to prove their efficacy and cost benefit. PAC will remain a gold standard for CO monitoring, however, use of newer devices based on pulse contour analysis, pulse pressure analysis and Doppler methods should be encouraged.

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Does manual thrombus aspiration help optimize stent implantation in ST-segment elevation myocardial infarction?

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treated with TA had less prevalence of multivessel disease (39.7% vs 54.7%, $P = 0.003$) and higher prevalence of initial thrombolysis in myocardial infarction flow < 3 ($P < 0.001$) than NTA group. There was a higher rate of direct stenting (58.7% vs 45.5%, $P = 0.009$), with shorter (24.1 ± 11.8 mm vs 26.9 ± 15.7 mm, $P = 0.038$) and larger stents (3.17 ± 0.43 mm vs 2.93 ± 0.44 mm, $P < 0.001$) in the TA group as compared to NTA group. The number of implanted stents (1.3 ± 0.67 vs 1.5 ± 0.84 , $P = 0.009$) was also lower in TA group.

CONCLUSION: In an "all-comers" STEMI population, the use of TA resulted in more efficient procedure leading to the implantation of less number of stents per lesion of shorter lengths and larger sizes.

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Key words: ST-segment elevation myocardial infarction; Primary percutaneous coronary intervention; Manual thrombus aspiration; Stent; Thrombolysis in myocardial infarction flow

Abstract

AIM: To evaluate the impact of thrombus aspiration (TA) on procedural outcomes in a real-world ST-segment elevation myocardial infarction (STEMI) registry.

METHODS: From May 2006 to August 2008, 542 consecutive STEMI patients referred for primary or rescue percutaneous coronary intervention were enrolled and the angiographic results and stent implantation characteristics were compared according to the performance of manual TA.

RESULTS: A total of 456 patients were analyzable and categorized in TA group (156 patients; 34.2%) and non-TA (NTA) group (300 patients; 65.8%). Patients

Core tip: Thrombus embolization is highly detected in ST-segment elevation myocardial infarction (STEMI) leading to unfavorable clinical outcomes. To prevent thrombus embolization, manual thrombus aspiration (TA) receives a high recommendation during primary percutaneous coronary intervention (PCI) by clinical practice guidelines. However, the TASTE trial, recently published, showing no impact of manual TA on short-term mortality, has reopened the debate about the role of this technique in STEMI. This study is one the first showing that manual TA optimizes stent implantation during primary PCI resulted in more efficient procedures, leading to the implantation of fewer, shorter and larger stents.

Fernández-Rodríguez D, Alvarez-Contreras L, Martín-Yuste V, Brugaletta S, Ferreira I, De Antonio M, Cardona M, Martí V, García-Picart J, Sabaté M. Does manual thrombus aspiration help optimize stent implantation in ST-segment elevation myocardial infarction? *World J Cardiol* 2014; 6(9): 1030-1037 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v6/i9/1030.htm> DOI: <http://dx.doi.org/10.4330/wjc.v6.i9.1030>

INTRODUCTION

ST-segment elevation myocardial infarction (STEMI) occurs as a result of atherosclerotic plaque rupture or erosion and platelet and coagulation activation leading to thrombus formation and complete coronary occlusion^[1]. Primary percutaneous coronary intervention (PCI) with stent implantation is the preferred method to restore epicardial flow in STEMI^[2,3]. Several thrombectomy devices have been developed with the aim to avoid any suboptimal myocardial reperfusion related to thrombus embolization, which might lead to unfavorable clinical outcome^[4].

The randomized clinical trial (RCT) TAPAS, in particular, showed that manual thrombus aspiration (TA) improved myocardial reperfusion and reduced mortality in STEMI patients at 1-year follow-up^[5,6]. These results, confirmed by other studies^[7-10], including a meta-analysis^[11] of 11321 patients from 20 RCT showing lower rates of late mortality, reinfarction and stent thrombosis in patients underwent manual TA compared with conventional primary PCI, led to a recommendation class IIa for manual TA in patients undergoing primary PCI for STEMI^[12]. Nevertheless, the use of the thrombectomy devices is still controversial and not routine in STEMI patients, especially because some studies have shown no impact on clinical outcome^[13-20], such as the TASTE trial^[21]. This RCT, recently published, did not show any impact of manual TA on mortality or any of several other clinical outcomes at 30 d. Furthermore, the potential effect of TA on optimization of stent implantation has not been elucidated yet.

Therefore, we sought to investigate the factors which can lead to the use of the manual TA in STEMI and its impact on acute angiographic success and stent implantation characteristics in a real-world STEMI population.

MATERIALS AND METHODS

Study population

Between May 2006 and August 2008, all consecutive patients with STEMI referred to our hospital for primary or rescue PCI were enrolled. There were no exclusion criteria. Clinical and angiographic characteristics of all patients were prospectively collected. All patients signed a written informed consent prior to PCI procedure and agreed to be clinically followed. At the time of the study an IRB approval was not formally necessary for observational registries that use a CE-mark approved device.

Procedure

Patients treated with primary PCI were pretreated with aspirin (300 mg), clopidogrel loading dose (300 mg) and unfractionated heparin adjusted to weight. The use of glycoprotein (GP) IIb/IIIa inhibitors was left at the discretion of the operators in case of significant thrombus, slow or non-reflow of thrombotic complications. PCI was performed according to conventional clinical practice. Manual TA; using the 6-French Pronto V3[®] aspiration catheter (Vascular Solutions Inc, Minneapolis, MN) and the 6-French Export[®] aspiration catheter (Medtronic, Minneapolis, MN), was performed according to the operator's choice; and patients were thereafter classified in TA group and non-thrombus aspiration (NTA) group.

Manual TA technique was performed as follows. The aspiration was started 2-cm before the culprit lesion and the aspiration catheter was advanced very slowly, crossing the lesion with continuous aspiration. The catheter was removed under aspiration even into the guiding catheter, with generous backflow after retrieving the thrombectomy device. At least two or three passages were performed. Manual TA was especially considered, in case of high thrombus burden and initial slow thrombolysis in myocardial infarction (TIMI) flow.

Definitions and end-points

Time to treatment was defined as time from symptom onset to initial intracoronary therapy by TA or balloon inflation of the infarct-related coronary artery^[22].

TIMI flow grade was evaluated pre guide-wire and post-PCI^[6].

No-reflow was defined as a TIMI flow grade < 2 in absence of coronary dissection, coronary hematoma, occlusive coronary thrombosis or epicardial spasm^[10]. Thrombus embolization was defined as circumscribed filling defects and/or abrupt cut off of a vessel distal to the target lesion or in other coronary vessel on the angiogram after PCI^[23]. Coronary dissection was defined by the presence of a curvilinear filling defect parallel to the vessel lumen, contrast medium outside of the vessel lumen persisting after passage of contrast medium, or a spiral-shaped filling defect partially or totally obstructing the coronary artery lumen^[24].

ST was defined and categorized, according to Academic Research Consortium^[25]. Angiographic success was defined as final TIMI flow equals 3 plus absence of any angiographic complication.

The angiographic assessment was performed by consensus of two independent experienced interventional cardiologists. The primary end-point of this study was the rate of angiographic success, as above defined. Secondary end-points included technical and clinical issues related to the procedure as the number of implanted stents, the rates of direct stenting and post-dilatation, the maximal diameter of the implanted stents, the total stented length segment, the final TIMI flow and the resolution of the ST-segment elevation after primary PCI.

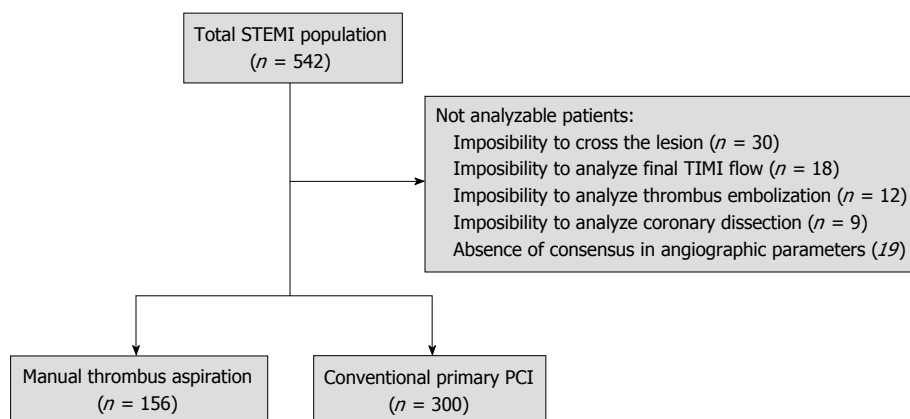


Figure 1 Study flowchart. STEMI: ST-segment elevation myocardial infarction; PCI: Percutaneous coronary intervention; TIMI: Thrombolysis in myocardial infarction.

Clinical follow-up

A clinical follow-up up to 3 years was performed by a clinical visit or telephone interview. Clinical outcomes were evaluated by measuring the rate of the major adverse cardiac events (MACE) defined as the combination of cardiac death, myocardial infarction (MI) and need for cardiac artery by-pass grafting (CABG) and its individual components, as well as the rate of all-cause death, and the need for target vessel and non-target vessel PCI revascularization. MI was defined according to the World Health Organization extended definition^[20].

Statistical analysis

Continuous variables were explored for normal distribution with the Kolmogorov-Smirnov test. Normally distributed variables were expressed as mean (1 standard deviation) and non-normally distributed variables were expressed as median (inter-quartile range) and were compared using *t*-student or with Mann-Whitney tests as appropriate. Categorical variables were expressed as count (percentage) and were compared using the χ^2 test.

In order to exclude confounding factors in primary end-point (angiographic success), multivariable logistic regression models were fitted to assess independent predictors. The following variables were tested for the predictors of the primary end-point: manual TA, age, gender, smoking history, prior MI, primary PCI, Killip class > I, initial TIMI flow = 0, use of GP II b/IIIa inhibitors and the use of drug-eluting stents (DES). The result was reported as HR together with the 95%CI.

All *P* values were 2-tailed, with statistical significance set at a level of < 0.05. Statistical analyses were performed using SPSS Statistics 20.0 (SPSS Inc., Chicago, IL, United States).

RESULTS

Baseline clinical and angiographic features

A total of 542 patients were prospectively included during the recruitment period. Of them, 30 patients were not analyzable because impossibility to crossing the culprit lesion by the TA device and 56 patients because

inability to analyze the angiographic data. The remaining 456 patients were finally studied and classified in TA (*n* = 156) and NTA groups (*n* = 300) (Figure 1).

Baseline characteristics are presented in the Table 1. TA group exhibited lower prevalence of dyslipidemia (19.2% *vs* 30.7%, *P* = 0.009) and multivessel disease (39.8% *vs* 54.7%, *P* = 0.003) in comparison with NTA group. Conversely, TA was more often used in primary PCI (73.1% *vs* 68.7%, *P* = 0.013), in presence of initial TIMI flow < 3 (*P* < 0.001), and with concomitant use of GP II b/IIIa inhibitors (65.3% *vs* 50.6%, *P* = 0.012) in comparison with NTA group.

Procedural results

Main procedural results are presented in the Table 2. Patients included in TA group showed higher prevalence of angiographic success (78.8% *vs* 68%, *P* = 0.015) and better final TIMI flow (TIMI flow 3: 85.9% *vs* 78.3%, *P* = 0.04) in comparison with NTA group. Patients treated with TA received higher rate of direct stenting (58.7% *vs* 45.5%, *P* = 0.009), less number of stents implanted (1.3 ± 0.67 *vs* 1.5 ± 0.84 , *P* = 0.009), with larger (3.17 ± 0.43 mm *vs* 2.93 ± 0.44 mm, *P* < 0.001) and shorter sizes (24.1 ± 11.8 mm *vs* 26.9 ± 15.7 mm, *P* = 0.038). The use of DES was lower in the TA group (DES; 11.3% *vs* 16.3%, *P* = 0.008). In multivariate analysis, TA was associated with angiographic success (HR = 2.3; 95%CI: 1.2-4.3) (Table 3).

In-hospital and long-term outcomes

In-hospital and long-term data are presented in the Table 4. No difference in major cardiac events was observed between groups during hospitalization. The only difference was a significantly higher CK peak [2563 (1284-4542) UI/L *vs* 1517 (744-3816) UI/L, *P* = 0.02] observed by the use of TA.

At three years clinical follow-up (36 ± 7 mo), no differences between manual TA and conventional PCI were observed in the rates of MACE (17.0% *vs* 21.6%, *P* = 0.25), all-cause death (17.0% *vs* 19.6%, *P* = 0.5), cardiac death (8.3% *vs* 7.9%, *P* = 0.83), MI (6.8% *vs* 10%, *P* = 0.27), need for CABG revascularization (1.4% *vs* 3.5%, *P* = 0.39),

Table 1 Baseline clinical and angiographic features *n* (%)

Characteristics	Thrombus aspiration <i>n</i> = 156	Conventional PCI <i>n</i> = 300	<i>P</i> value
Age, mean ± SD	63.2 ± 12.8	64.3 ± 12.8	0.410
Female sex	38 (24.4)	62 (20.7)	0.370
Previous or current smoker	94 (60.3)	205 (68.3)	0.085
Hypertension	82 (52.6)	166 (55.3)	0.570
Dyslipidemia	30 (19.2)	92 (30.7)	0.009
Peripheral vasculopathy	9 (5.8)	19 (6.3)	0.800
Previous MI	10 (6.7)	36 (12.3)	0.065
Previous PCI	8 (5.1)	29 (9.7)	0.092
Previous CABG	2 (1.3)	10 (3.3)	0.190
Indication			0.013
Primary	114 (73.1)	206 (68.7)	
Rescue	42 (26.9)	94 (31.3)	
Classification			0.650
Anterolateral	69 (44.2)	133 (44.3)	
Inferoposterior	83 (53.2)	152 (50.7)	
Non-Q MI	3 (1.9)	12 (4)	
LBBB	1 (0.6)	3 (1)	
Killip			0.058
I	182 (86.3)	228 (76.5)	
II	13 (8.5)	35 (11.7)	
III	1 (0.7)	7 (2.3)	
IV	7 (4.6)	28 (9.4)	
Number of diseased vessels			0.003
1	94 (60.3)	136 (45.3)	
2	43 (27.6)	95 (31.7)	
3	19 (12.2)	69 (23)	
Infarct related artery			0.650
LAD	68 (43.6)	137 (45.7)	
LCx	15 (9.6)	35 (11.7)	
RCA	69 (44.2)	116 (38.7)	
LM	4 (2.6)	8 (2.75)	
Bypass	0	1 (0.3)	
GP II b/IIIa inhibitors			0.012
IABP	7 (4.5)	25 (8.4)	0.120

PCI: Percutaneous coronary intervention; MI: Myocardial infarction; CABG: Coronary artery by-pass graft; LBBB: Left bundle branch block; LAD: Left anterior descending; LCx: Left circumflex; RCA: Right coronary artery; LM: Left-main; IABP: Intra-aortic balloon pump; GP: Glycoprotein.

target vessel PCI revascularization (5.4% *vs* 8.9%, *P* = 0.2), and non-target vessel PCI revascularization (4.8% *vs* 5.7%, *P* = 0.68) and definite ST (1.4% *vs* 4.4%, *P* = 0.15).

DISCUSSION

The major findings of this study were: (1) manual TA was used more often in primary PCI and in patients with worse TIMI flow; (2) its use was subsequently related to optimization of procedural technique; and (3) TA was independently associated with acute angiographic success.

Optimization of angiographic outcomes and stent implantation by manual TA in real-world

According to clinical trials and real-world registries, our work confirms that manual TA is more often used in the

Table 2 Procedural data and angiographic results *n* (%)

Characteristics	Thrombus aspiration <i>n</i> = 156	Conventional PCI <i>n</i> = 300	<i>P</i> value
Time to treatment, median (IQR)	273 (170-477)	300 (180-480)	0.610
Initial TIMI flow			< 0.001
0	111 (71.2)	143 (48.8)	
1	9 (5.8)	16 (5.5)	
2	16 (10.3)	38 (13)	
3	20 (12.8)	96 (32.8)	
Initial TIMI flow < 3	136 (87.2)	204 (67.2)	< 0.001
Final TIMI flow			0.140
0	2 (1.3)	9 (3.1)	
1	1 (0.6)	6 (2.1)	
2	19 (12.3)	50 (17.1)	
3	133 (85.8)	227 (77.7)	
Final TIMI flow < 3	22 (14.1)	65 (21.7)	0.040
Angiographic complication			0.450
Non-reflow	6 (3.8)	16 (5.4)	
Thrombus embolization	7 (4.5)	22 (7.4)	
Coronary dissection	2 (1.3)	7 (2.4)	
Angiographic success	123 (78.8)	200 (68)	0.015
Direct stenting	88 (58.7)	131 (45.5)	0.009
Type of stent			0.008
BMS	133 (88.7)	238 (79.3)	
DES	17 (11.3)	62 (20.7)	
Length of stented segment (mm), mean ± SD	24.1 ± 11.8	26.9 ± 15.7	0.038
Diameter of stented segment (mm), mean ± SD	3.17 ± 0.43	2.93 ± 0.44	< 0.001
Number of stents, mean ± SD	1.3 ± 0.67	1.5 ± 0.84	0.009
LVEF, mean ± SD	49.6 ± 9.8	49 ± 10.4	0.610

PCI: Percutaneous coronary intervention; IQR: Interquartile range; TIMI: Thrombolysis in myocardial infarction; BMS: Bare metal stents; DES: Drug-eluting stents; LVEF: Left ventricle ejection fraction.

presence of high thrombus burden, such as in patients with initial low TIMI flow (0-1) or primary PCI indication. This registry confirms as well that use of TA achieves better angiographic results than conventional PCI, with greater reduction in thrombus burden and higher rate of final TIMI flow 3. Of note is the recent article by Ahn *et al*^[27] which showed that the addition of II b/IIIa inhibitors (Abciximab) to manual TA improves the index of micro-circulatory resistance and the microvascular obstruction assessed by cardiac magnetic resonance. This leads us to hypothesize that the optimal strategy to optimize myocardial perfusion would be the synergistic use of these two therapeutic options.

Moreover, it appeared that the use of TA allowed immediate good angiographic results before stent implantation, so that fewer, larger and shorter stents could be more often implanted. Previous clinical trials and real-world registries failed to show any differences in the length, diameter and number of implanted stents be-

Table 3 Multivariate analysis of angiographic success

	HR (95%CI)	P
Thrombus aspiration	2.3 (1.2-4.3)	0.007
Primary PCI	4.4 (2.1-9)	< 0.001
Active smoking	1.76 (0.9-3.4)	0.093
Age	1.031 (1.001-1.063)	0.044
Initial TIMI flow = 0	0.46 (0.25-0.84)	0.012

PCI: Percutaneous coronary intervention; TIMI: Thrombolysis in Myocardial Infarction.

Table 4 In-hospital and long-term outcomes n (%)

	Thrombus aspiration n = 156	Conventional PCI n = 300	P value
In-hospital			
CK peak UI/L, median (IQR)	2563 (1284-4542)	1517 (744-3816)	0.020
ST resolution at 30 min	75 (71.4)	174 (74)	0.610
Intra-procedural death	2 (1.3)	5 (1.7)	1.000
In-hospital cardiac death	15 (9.6)	22 (7.3)	0.400
Non-target vessel PCI revascularization CABG	12 (7.7)	41 (13.8)	0.059
	0 (0)	1 (0.3)	1.000
Follow-up			
MACE	25 (17.0)	61 (21.6)	0.250
All-cause death	26 (17.0)	57 (19.6)	0.500
Cardiac death	13 (8.3)	23 (7.9)	0.830
MI	10 (6.8)	28 (10)	0.270
CABG	2 (1.4)	10 (3.5)	0.390
Target vessel PCI revascularization	8 (5.4)	25 (8.9)	0.200
Non-target vessel PCI revascularization	7 (4.8)	16 (5.7)	0.680
Definitive stent thrombosis	2 (1.4)	12 (4.4)	0.150
Probable stent thrombosis	1 (0.7)	2 (0.7)	1.000
Possible stent thrombosis	2 (1.4)	6 (2.2)	0.720

PCI: Percutaneous coronary intervention; CABG: Coronary artery by-pass graft; MACE: Major adverse cardiac events; MI: Myocardial infarction; IQR: Interquartile range; ST: Stent thrombosis.

tween patients treated with or without TA^[6,7,10,20,28] except for one brief work^[29] that demonstrated a higher stent diameter after manual TA, in STEMI patients treated with bare metal stents. Recently, the TASTE trial^[21] also showed the need for fewer stents per procedure in manual TA group in comparison with conventional PCI. It is well known that intra-stent restenosis and ST are directly related to the characteristics of the stents^[30,31]. Thus; optimizing on stent implantation using fewer stents and stents of larger diameter and smaller length, during STEMI could have long-term prognostic implications by reducing the intra-stent restenosis and ST.

Besides, in light of these results we might hypothesize that TA may be cost-saving. Therefore, further studies on

cost-effectiveness implications by the use of manual TA in primary PCI are warranted.

Clinical outcomes of TA in real-world

This registry reflected real-world clinical practice in STEMI population as no exclusion criteria was applied. Additionally, both primary and rescue PCI patients were included.

Unlike other studies with strict inclusion criteria^[6,10], this registry demonstrated no impact of TA on both short and long-term outcomes. In the TAPAS trial^[5,6], only patients with primary PCI were included; in another real-world registry^[10], only patients with primary PCI indication and TIMI flow 0-1 were included. Conversely, our clinical results are consistent with studies with broad inclusion criteria, such as the TASTE trial^[21], that evaluated the primary end-point at short-term and with the largest published real-world registry in manual TA^[20] that had a very extended follow-up. Both studies included patients with initial TIMI flow from 0 to 3 and rescue or primary PCI indication. Thus, differences in inclusion criteria and in follow-up periods between the various trials and inherent selection bias induced in clinical registries may explain the different impact of the TA on long-term outcome.

Furthermore, it is noteworthy that in our study MACE rate was numerically higher in NTA group, although it did not reach statistical significance, probably due to the small number of patients included in our registry.

Of note is that no difference in target-vessel revascularization or stent thrombosis was found between the two groups, despite implantation of larger and shorter stent in TA than NTA group: this finding may be explained by the higher rate of DES implanted in NTA group than TA group.

This interesting controversy will continue until the publication of the results of the TOTAL trial^[32]. The TOTAL trial is a multicenter, prospective, open, international, randomized trial with blinded assessment of outcomes which will recruit 10700 STEMI patients to compare routine manual TA with the Export aspiration catheter *vs* conventional primary PCI alone. The primary outcome will be the composite of cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or new or worsening New York Heart Association class IV heart failure up to 180 d.

Study limitations

First, this study is a non-randomized, prospective registry and there were differences in baseline clinical and angiographic characteristics that could lead to a worse baseline risk profile in NTA group. Second, the use of GP II b/IIIa inhibitors was higher in the TA group and this difference could also affect angiographic results in this group. Third, in our study manual TA was only used in one third of cases, whereas current use of manual TA in recent all-comer RCT^[33-35] is around two thirds of patients. This was related to the relatively lack of evidence of manual thrombectomy at the time of the recruitment of the registry. Fourth, the relative small number of patients

included in our study could preclude any conclusions regarding clinical efficacy of TA.

In this all-comer registry, TA was able to optimize stent implantation technique, leading to the implantation of less number of stents per lesion of shorter lengths and larger sizes, and was associated with angiographic success following PCI for STEMI.

COMMENTS

Background

In ST-segment elevation myocardial infarction (STEMI) patients, manual thrombus aspiration (TA) is effective to reduce thrombus burden. Nevertheless, the effect on optimization of stent implantation has not been elucidated yet. Therefore, the objective of this study is to evaluate the impact of manual TA on acute angiographic success and stent implantation characteristics in a real-world STEMI.

Research frontiers

Manual TA reduces thrombotic burden, receiving a recommendation class IIa during the performance of primary percutaneous coronary intervention. However, the TASTE trial, recently published, showing no impact of manual TA on 30-d mortality, has reopened the debate about the role of this technique in STEMI setting.

Innovations and breakthroughs

Thrombus embolization is detected up to 15% of STEMI population and is responsible for suboptimal myocardial reperfusion, leading to unfavorable clinical outcomes. Manual TA reduces thrombotic burden and receives a high recommendation during the performance of primary percutaneous coronary intervention. The TASTE trial, demonstrating absence of impact of manual TA on short-term mortality, has reopened the debate about the use of this technique in STEMI patients. In the present study the authors want to investigate, in a real-world STEMI population, the factors which can lead to the use of manual thrombectomy in STEMI and its impact on angiographic and stent implantation characteristics.

Applications

The study results suggest that manual TA during primary percutaneous coronary intervention is associated with a higher rate of angiographic success and optimization on stent implantation compared with conventional primary percutaneous coronary intervention, in a real-world population. However, it seems to have no impact on long-term clinical outcomes.

Terminology

STEMI: It is a type of acute coronary syndromes, which occurs when a coronary artery becomes totally blocked by a blood clot, causing the heart muscle supplied by the artery to die; Primary percutaneous coronary intervention: It is a non-surgical procedure used to open the occluded coronary arteries during STEMI; Manual TA device: It is a type of thrombectomy device, which comprises a monorail catheter with a central lumen connected proximally to a syringe for manual aspiration, designed to extract thrombotic material during percutaneous coronary intervention.

Peer review

In this study, Diego *et al* reported that the thrombus aspiration therapy in patients with AMI were associated with high procedure success and contributed to optimize the implantation of stents. As a non-randomized, prospective registry study, it provide their some new insights about the use of thrombus aspiration in the real world.

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Calcific left atrium: A rare consequence of endocarditis

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Author contributions: Dattilo G and Di Bella G undertook the patient clinical examination and echocardiogram; Casale M, Giugno V, Camarda L and Laganà N collected the patient's clinical data and wrote the paper; Anfuso C performed CT and CMR; Dattilo G and Di Bella G analyzed the data.

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Abstract

Usually, cardiac calcifications are observed in aortic and mitral valves, atrio-ventricular plane, mitral annulus, coronary arteries, pericardium (usually causing constrictive pericarditis) and cardiac masses. Calcifications of atrial walls are unusual findings that can be identified only using imaging with high spatial resolution, such as cardiac magnetic resonance and computed tomography. We report a case of a 43-year-old patient with no history of heart disease that underwent cardiac evaluation for mild dyspnoea. The echocardiogram showed a calcific aortic valve and a hyper-echogenic lesion located in atrio-ventricular plane. The patient was submitted to cardiac magnetic resonance and to computed tomography imaging to better characterize the localization of mass. The clinical features and location of calcified lesion suggest an infective aetiology causing an endocarditis involving the aortic valve, atrio-ventricular plane and left atrium. Although we haven't data to support a definite and clear diagnosis, the clinical features and location of the calcified lesion suggest

an infective aetiology causing an endocarditis involving the aortic valve, atrio-ventricular plane and left atrium. The patient was followed for 12 mo both clinically and by electrocardiogram and echocardiography without worsening of clinical, electrocardiographic and echocardiographic data. Cardiac magnetic resonance imaging and computed tomography are ideal methods for identifying and following over time patients with calcific degeneration in the heart.

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Key words: Endocarditis complications; Left atrium calcification; Cardiac magnetic resonance; Computed tomography

Core tip: A patient was submitted to echocardiography, cardiac magnetic resonance and to computed tomography imaging to better characterize a hyper-echogenic lesion located in the atrio-ventricular plane. The clinical features and location of the calcified lesion suggest an infective aetiology causing an endocarditis involving the aortic valve, atrio-ventricular plane and left atrium.

Dattilo G, Anfuso C, Casale M, Giugno V, Camarda L, Laganà N, Di Bella G. Calcific left atrium: A rare consequence of endocarditis. *World J Cardiol* 2014; 6(9): 1038-1040 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v6/i9/1038.htm> DOI: <http://dx.doi.org/10.4330/wjc.v6.i9.1038>

INTRODUCTION

Calcification can be observed in many cardiac localizations but is particularly rare as a lesion that involves the aortic valve, atrioventricular plane and left atrium.

CASE REPORT

We report a case of a 43-year-old patient with no history

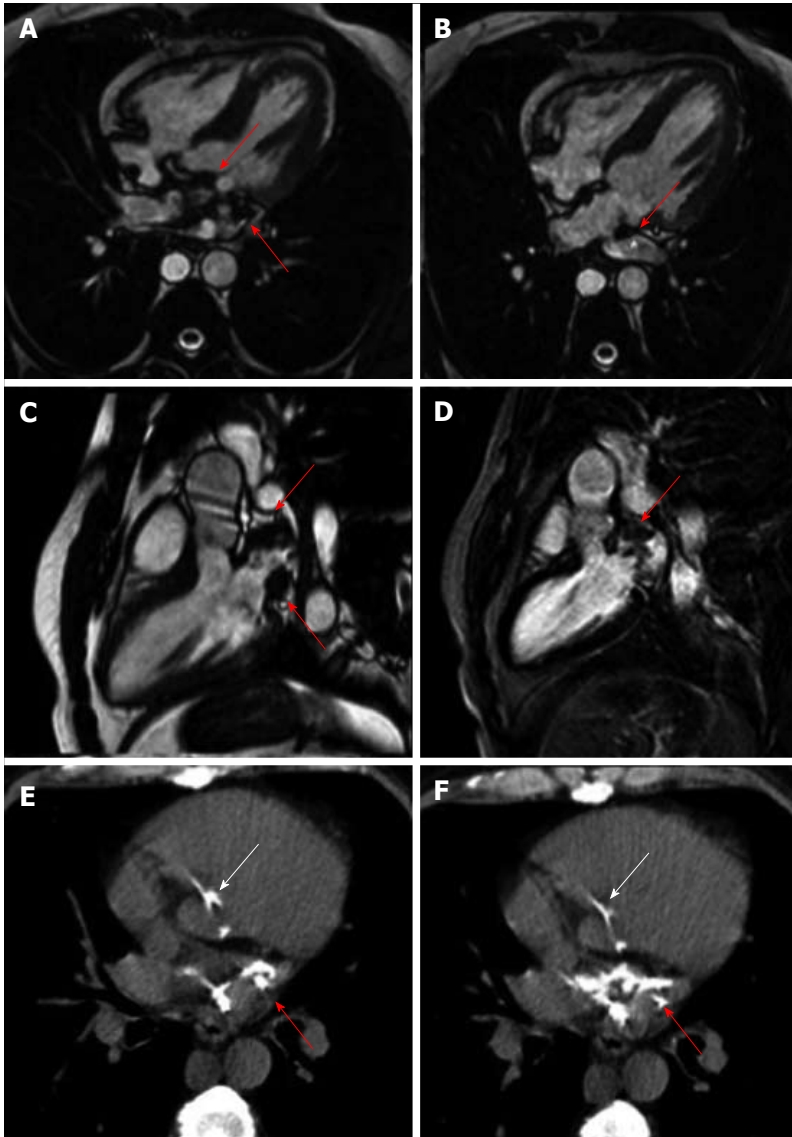


Figure 1 Photograph. A-D: Cardiac magnetic resonance showed hypointense areas located in left atrium and atrio-ventricular plane (red arrows); B: Partial obstruction of superior pulmonary vein; E and F: Cardiac computed tomography showed the presence of a mass suggestive of calcium in left atrium (red arrows), atrioventricular groove and aortic left ventricular outflow (white arrows).

of heart disease who underwent cardiac evaluation for mild dyspnoea. On physical examination he showed only a mild aortic systolic murmur. Blood pressure (130/65 mmHg) and electrocardiogram were normal. The echocardiogram showed an increase of left ventricular (LV) outflow aortic velocity (max velocity 2.2 m/s) due to calcific aortic valve and a hyper-echogenic lesion located in the atrio-ventricular plane. The patient was submitted to cardiac magnetic resonance (CMR) and to computed tomography imaging to better characterize the localization of mass.

CMR by steady-state free precession sequence showed normal atrial and ventricular dimensions; furthermore hypointense areas located in the left atrium and atrio-ventricular plane (Figure 1, red arrows on panel A-D) with a partial obstruction of superior pulmonary vein (Figure 1, on panel B) were found. A gradient echo T1-weighted image after 10 min of injection of contrast media (delayed

contrast enhancement technique) showed a hypointense area in left atrial (LA) suggesting calcium.

Axial images by cardiac computed tomography showed the presence of a mass suggestive of calcium in LA (Figure 1, red arrows on panel E-F), atrioventricular groove and aortic LV outflow (white arrows on panel E-F).

The patient was followed for 12 mo both clinically and by electrocardiogram and echocardiography without worsening of clinical, electrocardiographic and echocardiographic data.

DISCUSSION

Calcification can be observed in many cardiac localizations^[1-7]; particularly, they can be located: (1) valves (usually aortic and mitral valve); (2) atrio-ventricular plane; (3) mitral annulus (usually located in mitral posterior annulus as consequence of a degenerative disorders in the elderly,

osteoporosis women, kidney disease); (4) epicardial coronaries; (5) cardiac masses (caseous calcification of the posterior mitral annulus, soft tissue calcified sarcomas, calcified echinococcus cysts, cardiac osteochondromas and cardiac calcified amorphous tumors); and (6) in pericardium (usually causing constrictive pericarditis).

The calcifications of atrial walls are unusual findings that can be identified only using imaging with high spatial resolution, such as cardiac magnetic resonance and computed tomography. Cardiac magnetic resonance imaging and computed tomography, having a high spatial resolution and tissue characterization, are ideal methods for identifying and following over time patients with unusual localization of calcific degeneration in the heart. This case report represents a very rare manifestation of extended endocarditis. Although we haven't data to support a definite and clear diagnosis, the clinical features and location of the calcified lesion suggest an infective aetiology causing an endocarditis involving the aortic valve, atrio-ventricular plane and left atrium.

COMMENTS

Case characteristics

A 43-year-old patient with no history of heart disease who underwent cardiac evaluation for mild dyspnoea.

Clinical diagnosis

At physical examination there was only a mild aortic systolic murmur.

Imaging diagnosis

Cardiac magnetic resonance (CMR) by steady-state free precession sequence showed hypointense areas located in the left atrium and atrio-ventricular plane with a partial obstruction of the superior pulmonary vein and the delayed contrast enhancement technique showed a hypointense area in left atrial (LA) suggesting the presence of calcium. Axial images by cardiac computed tomography showed the presence of a mass suggestive of calcium in LA, atrioventricular groove and aortic left ventricular outflow.

Related reports

Endocarditis is a serious condition that can endanger patient life, showing itself in different ways.

Term explanation

CMR delayed contrast enhancement technique is based on the use of gradient echo T1-weighted images 10 min after the injection of contrast medium and it

is very useful to evaluate the tissue characteristics, particularly in an organ in constant motion like the heart.

Experiences and lessons

This case report not only represents one of the largest extensions of endocarditis described but also shows a lack of correlation between clinical manifestation and clinical symptoms.

Peer review

The report is interesting, and it is an excellent work.

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Systemic venous atrium stimulation in transvenous pacing after mustard procedure

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lead usually screwed into the left atrial appendage. The case presented demonstrates that, when the systemic venous atrium is separate from the left atrial appendage, the lead can be easily and safely placed in the systemic venous left atrium gaining satisfactory sensing and pacing thresholds despite consisting partially of pericardial tissue.

Puntrello C, Lucà F, Rubino G, Rao CM, Gelsomino S. Systemic venous atrium stimulation in transvenous pacing after mustard procedure. *World J Cardiol* 2014; 6(9): 1041-1044 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v6/i9/1041.htm> DOI: <http://dx.doi.org/10.4330/wjc.v6.i9.1041>

Abstract

We present the case of a young woman corrected with a Mustard procedure undergoing successful transvenous double chamber pacemaker implantation with the atrial lead placed in the systemic venous channel. The case presented demonstrates that, when the systemic venous atrium is separate from the left atrial appendage, the lead can be easily and safely placed in the systemic venous left atrium gaining satisfactory sensing and pacing thresholds despite consisting partially of pericardial tissue.

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Key words: Cardiac pacing; Mustard procedure; Transposition of great arteries

Core tip: Disturbances of rhythm in patients undergoing Mustard Procedure are common and they often require implantation of a permanent pacemaker with the atrial

INTRODUCTION

The mustard operation (MO)^[1] was a well-established method to correct the transposition of the great arteries before being superseded, in the recent years, by anatomic repair, the so called arterial switch operation^[2,3]. The procedure employs a pericardial baffle to change the direction of the blood flow from the systemic venous return to the left ventricle and pulmonary venous return to the right ventricle^[1].

Disturbances of rhythm and conduction in patients undergoing MO have been the focus of many studies^[4-6]. Occasionally a permanent pacemaker is needed especially for patients with symptomatic sick sinus syndrome.

Usually one electrode is put in the apex of the anatomic left (subpulmonary) ventricle and the atrial lead is fixed into the left atrial appendage^[4].

Nonetheless, if the systemic venous atrium does not include the left atrial appendage it is impossible to screw the atrial lead into the left atrial appendage. In addition, it is questionable whether, positioning the electrode in the systemic venous atrium, sensing capabilities are inadequate as the neo-atrium consists partially of

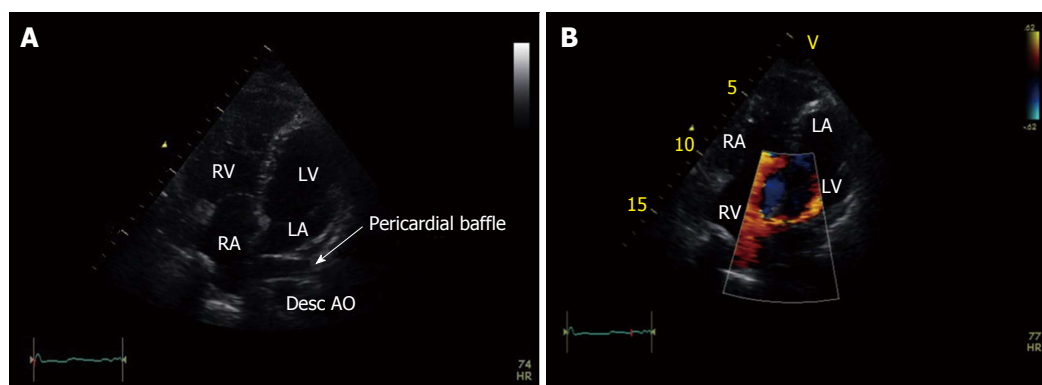


Figure 1 Apical 4-chamber view. A: The Mustard procedure employs a pericardial baffle to direct systemic venous return to the left ventricle and pulmonary venous return to the right ventricle; B: With color Doppler. The deoxygenated blood from the vena cavae is directed to the mitral valve and thence into the left ventricle which is the pumping ventricle for the pulmonary artery and the pulmonary circulation. LV: Left ventricle; RV: Right ventricle.

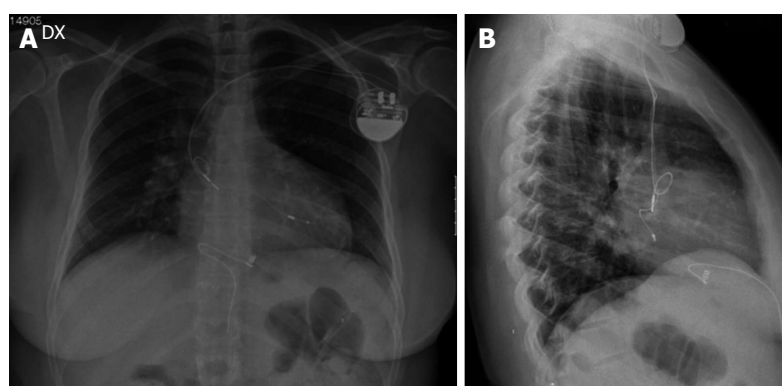


Figure 2 Chest X-ray. A: Antero-posterior chest X-ray after pacemaker implantation to confirm the position of the pacemaker leads. The ventricular lead is situated in the anatomic left ventricle, and the atrial lead in the systemic venous baffle; B: Lateral chest X-ray after pacemaker implantation to confirm the position of the pacemaker leads. In this patient the left atrial appendage was kept outside of venous tissue therefore the atrial lead was inserted and screwed into the systemic venous channel and a loop was created.

pericardial tissue and whether the electrode remains in the correct position.

We present the case of a young woman corrected with a Mustard procedure undergoing successful transvenous double chamber pacemaker implantation with the atrial lead placed in the systemic venous channel.

CASE REPORT

A 32-year-old female was born with a transposition of the great arteries (TGA), a large defect of the ventricular septum and a persistent ductus. At six months old she had a MO which involved closure of the defect of the ventricular septum and ductus arteriosus.

After the operation, she showed no symptoms at regular outpatient clinics. Nonetheless, 31 years after the MO she experienced dizziness, progressive tiredness, and shortness of breath. Echocardiography revealed a good left and right ventricular function (Figure 1).

With Holter monitoring we observed periods of atrioventricular junctional escape rhythm, high degree of atrioventricular block and pauses of up to 5.4 s. Indication was given for a pacemaker implantation. Due to the dizzy spells caused by sinus node dysfunction in addition

to atrioventricular conduction disturbances, the patient was subjected to a transvenous double chamber pacemaker implantation. Through the left cephalic vein an active-fixation electrode was introduced and placed in the apex of the anatomic left (subpulmonary) ventricle. Satisfactory values of sensing (8 mV) and pacing thresholds (0.5 mV) were gained without diaphragmatic stimulation.

In this patient the left atrial appendage was kept outside of venous tissue and therefore the passive-fixation atrial lead was inserted into the systemic venous channel and a loop was created.

Sensing and pacing thresholds were 1 mV and 2 V per 0.5 ms respectively. Post-procedural X-ray confirmed adequate positioning of the leads (Figure 2). The patient was discharged after an uneventful postoperative course.

At the 5-year follow up the leads were still in the correct position and sensing and pacing values were not subject to change. The woman was asymptomatic in sinus rhythm with a regular ventricular activation driven from the atrium.

DISCUSSION

TGA accounts for 5% to 7% of all congenital heart

Table 1 Potential technical and procedure-related complications of pacing following Mustard procedure

Complications
Lead dislodgement
Lead positioning
Abnormal anatomy post surgery
Spontaneous systemic venous baffle and venous obstruction
Systemic venous baffle and venous obstruction after lead insertion
Ventricular rhythm disturbances
Pacing thresholds, pacing impedance and sensing inadequate measurements or variations
System erosion/infection
Endocarditis risk
Paradoxical thromboembolic events

anomalies^[7]. The surgical repairs for TGA were first introduced by Senning in 1959; Mustard modified this technique in 1964^[1].

At the moment an anatomical correction is the most extensively used procedure; and the arterial switch has largely taken the place of the atrial switch procedure. Nonetheless late development of both atrial arrhythmias are well recognized late complications of atrial baffle surgery^[4-11] (Table 1).

Intra-atrial re-entrant tachycardia is the most common arrhythmia found among these patients, which has been associated with development of heart failure and death^[5,9].

In particular, causes of arrhythmias after the Mustard repair include^[4,12,13]: (1) damage during surgery to the sinus node or sinus node artery; (2) break of intra-atrial conduction by interruption of internodal pathways; and (3) intraoperative damage to atrioventricular (AV) node conduction tissue.

Pacemaker implantation is indicated for patients after MO who have a HR < 30 beats/min, Stokes-Adams episodes, patients requiring pharmacological therapy for tachyarrhythmias, or those with a poor systemic ventricular function and bradycardia^[14,15]. In addition, some MO patients require pacemaker implantation for sinus node dysfunction, AV block, in order to permit medical therapy of tachyarrhythmias or as an anti-tachycardia therapy^[16].

Pacemaker implantation in this setting can be technically challenging because of the complex anatomy^[17] and the possibility of complications such as systemic venous baffle obstruction or left innominate vein, right/left subclavian vein obstruction^[18]. Therefore, the determination of the exact vascular anatomy is mandatory to decide the most suitable position for placing the leads.

In this regard echocardiography, venography or intra-venous digital subtraction angiography before implantation may be of great help in studying the anatomy structural variations before pacemaker implantation.

However, usually one electrode is placed in the apex of the anatomic left (subpulmonary) ventricle and the atrial lead is fixed to the left atrial appendage^[7]. Berul *et al.*^[19] suggests, in the postoperative Mustard procedure,

that the superior aspect of the systemic venous-left atrium is the most optimal location.

Nonetheless, when left atrial appendage is not in place or it is not included into the systemic venous atrium, it is impossible to screw the atrial lead into the left atrial appendage. The electrode may be positioned in the systemic venous atrium but, as it consists partially of pericardial tissue, there are concerns associated with obtaining sub-optimal sensing and pacing thresholds and, despite this, there are no studies addressing the feasibility and efficacy of transvenous leads implanted into the pericardial baffle.

We present the case of a 32-year-old female undergoing a Mustard operation at six months of age who had transvenous double chamber pacemaker implantation because of high-degree atrioventricular block.

The ventricular electrode was placed in its usual position in the apex of the anatomic left (subpulmonary) ventricle avoiding creating a loop in this location which can be a substrate for ventricular ectopic beats^[4]. In contrast, since the left atrial appendage was outside the systemic venous atrium, it was impossible to place the lead into the left auricular appendix. Therefore, the atrial lead was positioned in the systemic venous channel and a passive fixation pacing was chosen to avoid pericardial baffle damage. Nonetheless, the use of passive-fixation pacing may lead to electrode dislodgement and this risk is raised by the absence of trabecular structures in the systemic venous channel differently from the left atrial appendage. Therefore, to prevent lead dislodgement, we created an electrode loop in the tube-like systemic venous channel.

At the end of the procedure sensing and pacing thresholds were adequate and, after 5 years, leads were still in the correct position with unchanged sensing and pacing thresholds.

In conclusion, the case of our patient demonstrates that in patients after Mustard repair, when the left atrial appendage is not reachable for surgical or anatomical reasons, the lead can be easily and safely placed in the systemic venous left atrium gaining satisfactory sensing and pacing thresholds and with no risk of lead dislodgement.

ACKNOWLEDGMENTS

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COMMENTS

Case characteristics

A 32-year-old female born with a transposition of the great arteries (TGA), a large ventricular septal defect and a patent ductus arteriosus who underwent a mustard operation (MO) at six months of age.

Clinical diagnosis

Progressive fatigue and dizziness and shortness of breath 31 years after her operation.

Differential diagnosis

Mobitz I second-degree atrioventricular (AV) block from Mobitz II second-degree AV block, as well as Mobitz II second-degree AV block from third-degree AV block.

Imaging diagnosis

Echocardiography, venography or intravenous digital subtraction angiography prior to implantation may be of great help in studying the anatomical structural variations before pacemaker implantation.

Pathological diagnosis

Holter monitoring showed episodes of atrioventricular junctional escape rhythm and high degree atrioventricular block.

Treatment

Indication was given for a pacemaker implantation.

Related reports

Some MO patients require pacemaker implantation for sinus node dysfunction, AV block, to permit medical therapy of tachyarrhythmias or as anti tachycardia therapy.

Term explanation

Mustard Operation is surgical treatment of TGA nowadays an anatomical correction is more preferred and this arterial switch procedure has largely replaced MO.

Experiences and lessons

The case presented demonstrates that, when the left atrial appendage is not included into the systemic venous atrium, the lead can be easily and safely placed in the systemic venous left atrium gaining satisfactory sensing and pacing thresholds despite it consists partially of pericardial tissue.

Peer review

A well-written case report merits consideration for publication as it describes a novel idea for permanent pacing in a patient with Mustard procedure.

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Acute myocarditis triggering coronary spasm and mimicking acute myocardial infarction

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spasm is an uncommon association, it is important to recognize it, particularly for the management for those patients presenting with ST-segment elevation and suspect myocardial infarction and angiographically normal coronary arteries. The present report highlights the role of cardiovascular magnetic resonance imaging to identify acute myocarditis as the underlying cause.

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Key words: Myocarditis; Acute coronary syndrome; Coronary spasm; Myocardial infarction

Core tip: The present report highlights the role of cardiovascular magnetic resonance imaging to identify acute myocarditis as the underlying cause of coronary spasm presenting with ST-segment elevation myocardial infarction in a young healthy man.

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Abstract

A 24-year-old healthy man consulted to our center because of typical on-and-off chest-pain and an electrocardiogram showing ST-segment elevation in inferior leads. An urgent coronary angiography showed angiographically normal coronary arteries. Cardiovascular magnetic resonance imaging confirmed acute myocarditis. Although acute myocarditis triggering coronary

INTRODUCTION

Myocarditis has been frequently associated in patients with acute chest pain syndrome and angiographically normal coronary arteries^[1]. When the clinical presentation plus dynamic electrocardiographic (ECG) changes is quite suggestive of an acute coronary syndrome, coronary angiography is currently the first imaging diagnostic assessment in this setting. As a complementary imaging tool, cardiovascular magnetic resonance (CMR) imaging

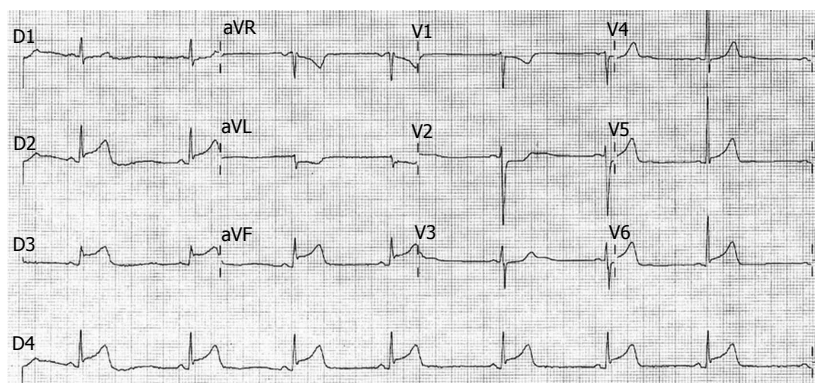


Figure 1 Twelve-lead electrocardiogram showing sinus rhythm with ST-segment elevation in the inferior leads and mirror image (mild ST-segment depression) in V1 to V3 and aVL.

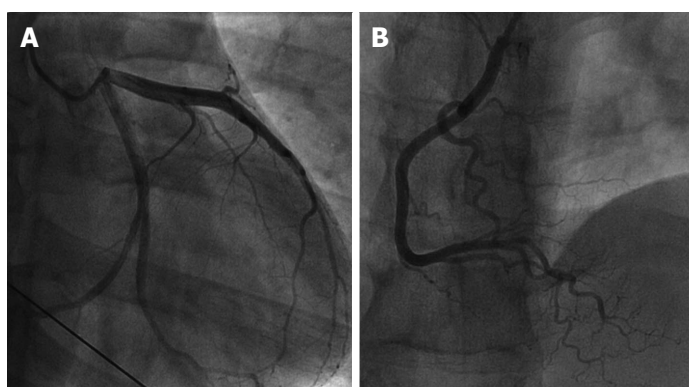


Figure 2 A and B coronary angiography showing angiographically normal coronary arteries.

provides a strong evidence for tissue characterization while completing the differential diagnosis.

CASE REPORT

A 24-year-old male consulted our emergency room complaining of 24 h of typical, intense on-and-off chest-pain. He had no previous medical history and no risk factors for coronary disease. There was no history suggesting a recent virus infection or drug use. During a chest pain episode in the emergency room, the ECG showed ST-segment elevation in the inferior leads (Figure 1). Troponin was positive on admission. An urgent coronary angiogram was performed showing angiographically normal coronary arteries (Figure 2), and the ECG normalized spontaneously. On the coronary care unit, 8-10 h after cardiac catheterization, the patient experienced a new episode of chest-pain with recurrence of inferior ST-segment elevation. A treatment with intravenous nitroglycerin was started which led to resolution of chest-pain and ST-segment normalization. Two-dimensional Doppler echocardiography showed a very mild infero-lateral hypokinesis with preserved left ventricular ejection fraction. Of note, the creatine kinase and the Troponin-I peaked at 1600 IU/L (normal value < 150 IU/L) and 51.8 micrograms/mL (normal value < 0.02 micrograms/mL) respectively, within 24 h. In order to characterize

the nature of this clinical scenario, the patient underwent CMR imaging confirming the mild infero-lateral hypokinesis (Figure 3A and B). In addition, tissue characterization showed myocardial edema localized in the epicardium of the lateral and infero-lateral walls (Figure 3C), the same area showed late gadolinium enhancement (Figure 3D). The subendocardial tissue appeared normal; therefore, highly compatible with acute myocarditis. The patient was discharged home seven days after admission on long acting Nifedipine and anti-inflammatory therapy.

DISCUSSION

Acute myocarditis triggering coronary vasospasm is a rare association. Especially myocarditis caused by Parvovirus B19, which affects endothelial cells, has been associated with coronary vasospasm^[2]. While coronary vascular smooth muscle cell dysfunction leading to Prinzmetal angina is an important differential diagnosis as well as coronary spasm on atherosclerotic coronary disease, myocarditis is an important but probably less frequent diagnosis to consider. The present report highlights the role of CMR imaging to identify acute myocarditis as the underlying cause. The epicardial distribution of edema and necrosis is a hallmark of myocarditis, as opposed to ischemic injury caused by epicardial coronary artery disease which necessarily leads to injury including the subendocardium^[3-6].

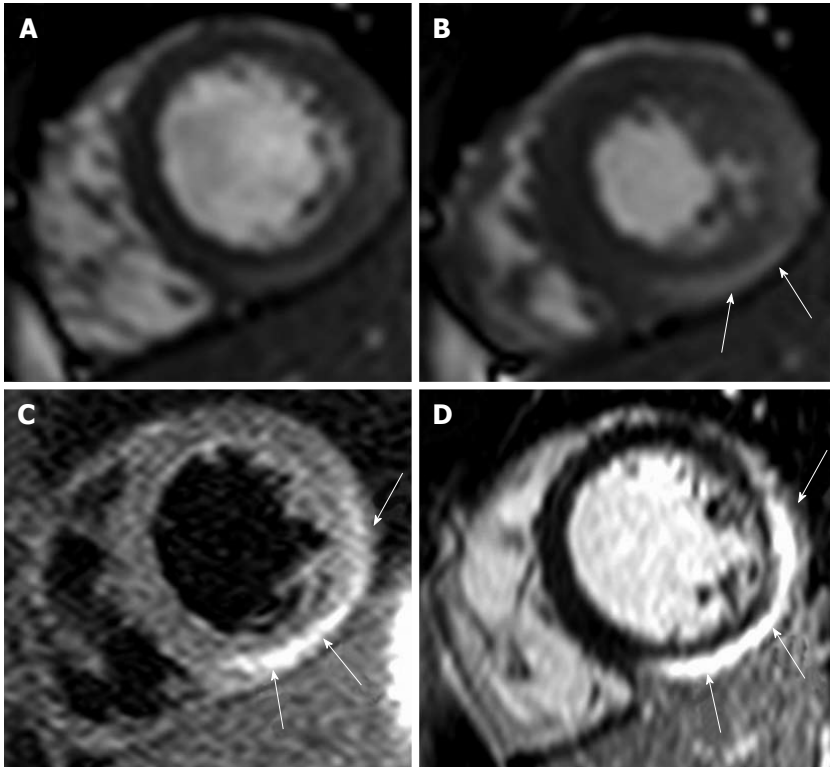


Figure 3 Cardiovascular magnetic resonance. Upper panel: Still frames of cine movies at end-diastole (A) and end-systole (B) showing mild infero-lateral hypokinesis (arrows); C: T2-STIR image showing myocardial edema in the lateral and inferior lateral epicardial wall (arrows); D: Gadolinium-enhanced image showing late enhancement predominately in the epicardial lateral and infero-lateral wall (arrows), highly compatible with acute myocarditis.

Myocarditis and epicardial coronary artery disease imply differences in medical treatment, therefore CMR enables the non-invasive assessment of changes in myocardial tissue composition (myocardial edema, hyperemia, and necrosis) and thus allowed for establishing the diagnosis of acute myocarditis^[3-6].

COMMENTS

Case characteristics

A healthy young man presenting with typical chest pain and an electrocardiogram showing inferior wall ST-elevation.

Clinical diagnosis

Acute myocardial infarction was the most likely clinical diagnosis given the description of chest pain and the electrocardiographic findings.

Differential diagnosis

Coronary vascular smooth muscle cell dysfunction leading to Prinzmetal angina as well as coronary spasm on atherosclerotic coronary disease are important differential diagnosis.

Laboratory diagnosis

Serial troponin levels progressively increased.

Imaging diagnosis

Coronary angiography demonstrated angiographically normal coronary arteries and cardiovascular magnetic resonance imaging showed myocardial edema localized in the epicardium of the lateral and infero-lateral walls, the same area showed late gadolinium enhancement.

Treatment

The patient was medically managed and discharged home seven days after admission on long acting Nifedipine and anti-inflammatory therapy.

Related reports

Myocarditis caused by Parvovirus B19, which affects endothelial cells, has been associated with coronary vasospasm.

Experiences and lessons

Although an uncommon association, it is important to recognize it, particularly for the management of those patients presenting with typical chest pain and electrocardiographic ST-segment elevation and therefore mimicking myocardial infarction.

Peer review

The authors present a case that reports an uncommon association of an acute myocarditis triggering coronary spasm and presenting as ST-elevation myocardial infarction. The manuscript is clearly written, well organized, comprehensive, appropriate referenced and concise in its content.

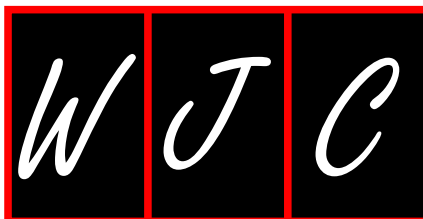
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- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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- 4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

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- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

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- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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- 7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

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- 8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

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- 9 Outreach: Bringing HIV-positive individuals into care. *HRS-A Careaction* 2002; 1-6 [PMID: 12154804]

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- 10 **Sherlock S**, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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- 11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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- 12 **Breedlove GK**, Schorheide AM. Adolescent pregnancy. 2nd ed. Wiczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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- 13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

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- 14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

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- 15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

Patent (list all authors)

- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee.

Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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Write as mean \pm SD or mean \pm SE.

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