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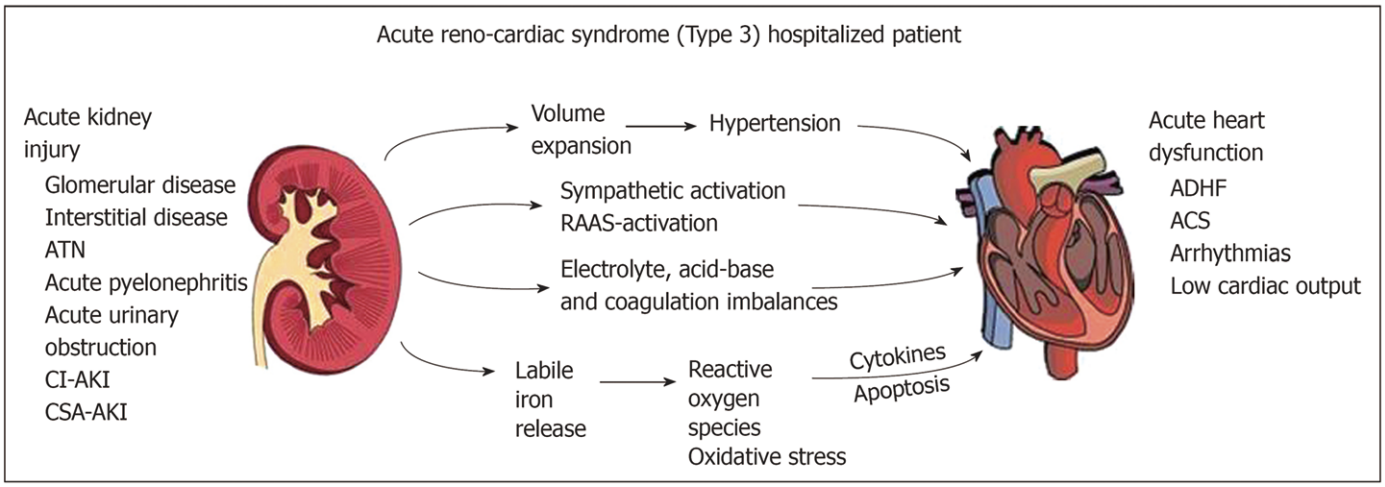

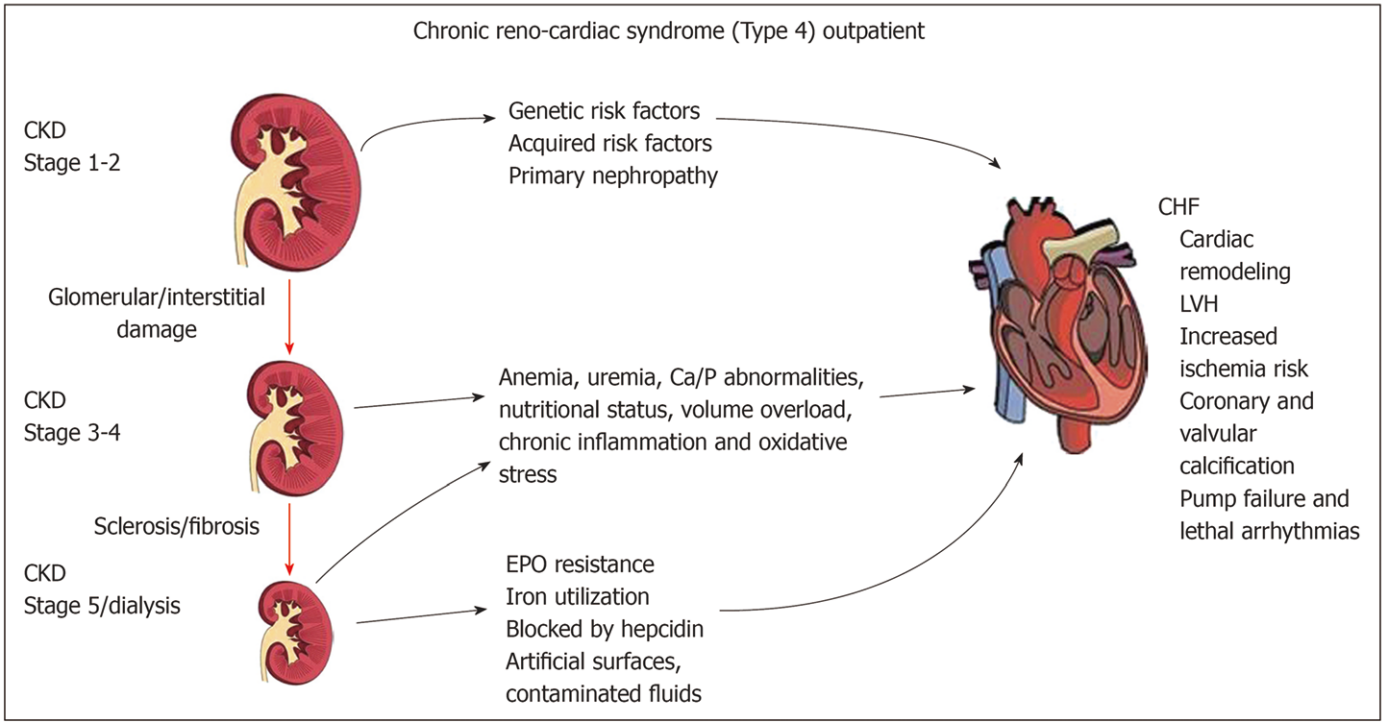

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EDITORIAL

Cardiorenal syndromes

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Abstract

Cardiorenal syndromes (CRS) have been subclassified as five defined entities which represent clinical circumstances in which both the heart and the kidney are involved in a bidirectional injury and dysfunction *via* a final common pathway of cell-to-cell death and accelerated apoptosis mediated by oxidative stress. Types 1 and 2 involve acute and chronic cardiovascular disease (CVD) scenarios leading to acute kidney injury or accelerated chronic kidney disease. Types 2 and 3 describe acute and chronic kidney disease leading primarily to heart failure, although it is possible that acute coronary syndromes, stroke, and arrhythmias could be CVD outcomes in these forms of CRS. Finally, CRS type 5 describes a simultaneous insult to both heart and kidneys, such as sepsis, where both organs are injured simultaneously. Both blood and urine biomarkers are reviewed in this paper and offer a considerable opportunity to enhance the understanding of the pathophysiology and known epidemiology of these recently defined syndromes.

Key words: Heart diseases; Kidney diseases; Cardiovascular diseases; Biological biomarkers; Creatinine

INTRODUCTION

Both cardiac and renal diseases commonly present in the same patient and have been associated with increased costs of care, complications, and mortality[1,2]. Cardiorenal syndromes (CRS), describing the dynamic inter-relationship between heart and kidney malfunction have been defined in a recent consensus process by the Acute Dialysis Quality Initiative (ADQI)[3]. This has generated five distinct syndromes upon which the epidemiology of CRS can be described. This paper will review this new classification and give concrete examples of each CRS, and discuss the available data on incidence and risk predictors. Finally, a succinct review of promising biomarkers will be presented that are very likely to change the described CRS epidemiological literature as we know it, based largely upon the measurement of a single blood biomarker-serum creatinine.

CLASSIFICATION OF CARDIORENAL SYNDROMES

The term cardiorenal syndromes suggests the presence of multiple syndromes with subtypes denoted by dysfunction of the principal organ (cardiac or renal or both) as well as the relative acuity of the condition. Both organs

must have or develop pathological abnormalities to fulfill the criteria for definition. The umbrella term "cardiorenal syndromes" was defined as "Disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other". Five subcategories of CRS are given below. Proposed pathophysiological mechanisms are described in Figure 1 for each syndrome.

POORLY LIGANDED, LABILE, CATALYTIC IRON AS THE BASIS OF OXIDATIVE STRESS REACTIONS

As shown in Figure 1, it has been recently determined that the process of oxidative stress resulting in cell dysfunction, accelerated apoptosis, and cell death is reliant on the cytosolic and extracellular presence of labile or catalytic iron. There are several steps in generation of reactive oxygen species (ROS). Oxygen may be reduced to form superoxide anion, which can then either dismutate or go through another reduction reaction by superoxide dismutase to form hydrogen peroxide which itself can then be reduced through several pathways. Overall, the net Fritz-Haber reaction is slow and in the presence of reduced transition metals such as ferric iron (Fe^{3+}), a Haber-Weiss reaction results in the formation of the highly damaging hydroxyl radical from the superoxide anion. Then in the presence of ferrous iron (Fe^{2+}), a Fenton-type reaction converts hydrogen peroxide to the highly damaging hydroxyl radical. Further reduction of the hydroxyl radical finally ends in the formation of water. It has been theorized that a common element to all forms of oxidative stress in the heart and kidneys involves the availability of unbound iron[4]. The body has an intricate management system for iron metabolism keeping it bound in transport proteins, heme, and cellular organelles for normal functioning[5,6]. If small amounts of iron are released from adjacent injured cells and not bound, this poorly liganded (labile or catalytic) iron in either the ferric or ferrous states, can facilitate the rapid generation of oxygen free radicals and the propagation of oxidative stress and injury across regions of vascular tissue[7]. Thus, it is possible that the fundamental pathophysiological basis for CRS is the loss of control over normal iron management after insults to either the heart or the kidneys in the form of hypoxia, chemotoxicity, or inflammation.

It has been interesting to note that intravenous infusions of iron in the form of iron dextran, iron sucrose, iron gluconate, and iron dextrin (polymaltose) have been proposed as a treatment for anemia in patients with heart failure. While in general the trials have demonstrated improvement in either anemia, symptoms, or both, there are as yet no published outcomes data[8]. Several studies have demonstrated that intravenous infusions of iron in normal volunteers and hemodialysis patients have resulted in a transient 3-4 fold rise in systemic levels of catalytic iron[9-11]. The clinical consequences of iron infusions and catalytic iron in heart failure (HF) patients, if any, are unknown at this time.

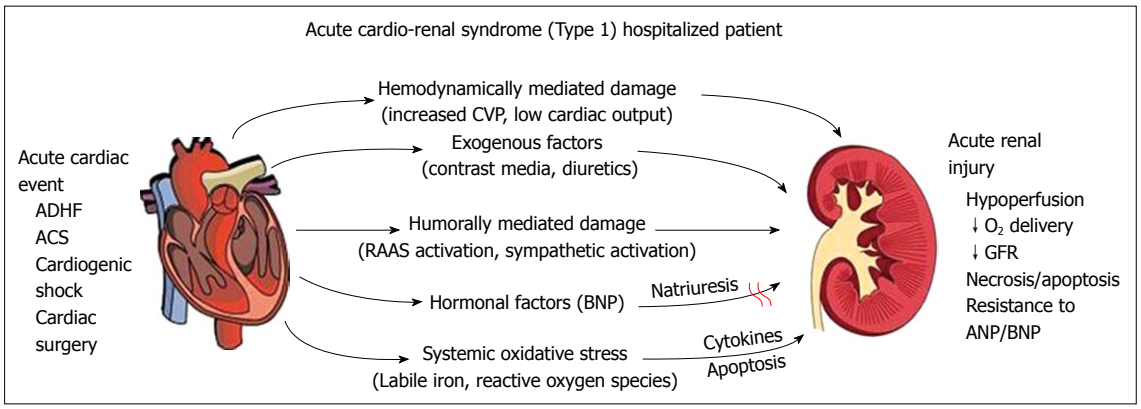
CATEGORIES OF SYNDROMES

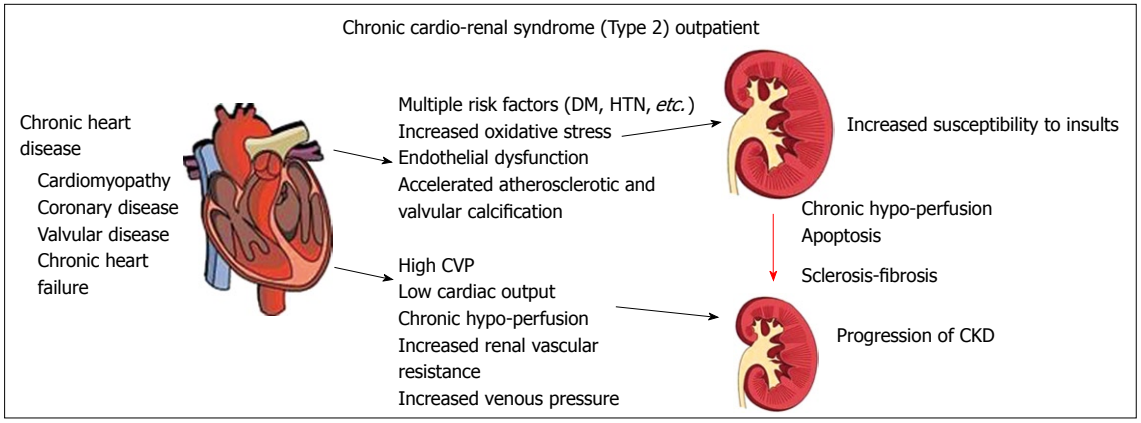
The broad and most important concepts of CRS include the following: (1) bidirectional organ injury or malfunction; (2) an inciting event for acute CRS; and (3) a precipitous decline in function for acute or chronic CRS.

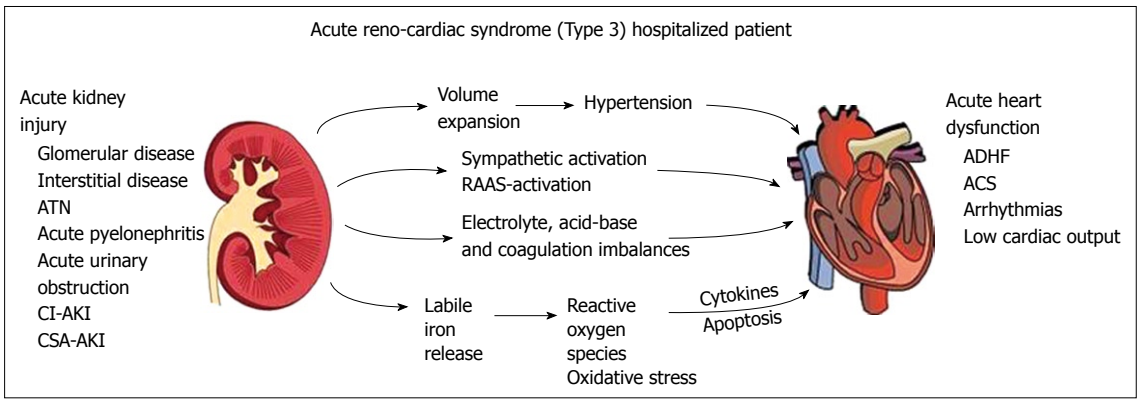
Acute cardiorenal syndrome

Acute cardiorenal syndrome (CRS Type 1): acute decompensation of cardiac function leading to acute renal failure. This is a syndrome of worsening renal function that frequently complicates acute decompensated heart failure (ADHF) and acute coronary syndrome (ACS). Seven observational studies have reported on the frequency and outcomes of CRS Type 1 in the setting of ADHF and five in ACS[4]. Depending on the population, 27%-40% of patients hospitalized for ADHF develop acute kidney injury (AKI) as defined by an increase in serum creatinine of $\geqslant$ 0.3 mg/dL[12,13]. Risk predictors for this complication include reduced baseline renal function, diabetes, and prior HF[13]. These patients experience more complicated hospital courses, longer inpatient stays, and higher mortality. In the Prospective Outcomes Study in Heart Failure (POSH) study, only in those with ADHF and a hospital course complicated by circulatory shock, hypotension, cardiac arrest, sepsis or ACS, a rise in serum creatinine did confer a higher 6-mo mortality[14]. Conversely, those with an increase in serum creatinine of $\geqslant$ 0.3 mg/dL but no other complications did not have higher mortality in the hospital, at 30 or 180 d. Thus, much of CRS Type 1 mortality is confounded by a complicated course and AKI. Importantly, it has been noted that CRS Type 1 in ADHF rarely occurs in the prehospital phase, and is observed after hospitalization, implying that some factor associated with hospitalization, namely diuresis, precipitates CRS. The use of loop diuretics, probably by further activation of the renin-angiotensin system and possibly worsening intra-renal hemodynamics, have been identified as one of the modifiable in-hospital determinants of CRS Type 1[15]. Testani *et al*[16] have recently shown in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial that the use of higher doses of loop diuretics, causing hemoconcentration, resulted in a 5-fold increased rate of worsening renal function. However, in this prospective trial of hemodynamic monitoring, aggressive diuresis was associated with a 69% reduction in mortality at 180 d. Several studies have now linked the presence of an elevated central venous pressure and renal venous congestion to the development of CRS Type 1, thus, the relative balance of venous and arterial tone and congestion of the kidney appear to be important in the drop in renal filtration that occurs during hospitalized treatment of ADHF[17].

The other major clinical scenario where CRS Type 1 develops is in the setting of urgent or elective coronary


Acute cardio-renal syndrome (Type 1) hospitalized patient
Acute cardiac event
ADHF
ACS
Cardiogenic shock
Cardiac surgery
Hemodynamically mediated damage
(increased CVP, low cardiac output)
Exogenous factors
(contrast media, diuretics)
Humorally mediated damage
(RAAS activation, sympathetic activation)
Hormonal factors (BNP)
Natriuresis
Systemic oxidative stress
(Labile iron, reactive oxygen species)
Cytokines
Apoptosis
Acute renal injury
Hypoperfusion
↓ O_2 delivery
↓ GFR
Necrosis/apoptosis
Resistance to ANP/BNP


Chronic cardio-renal syndrome (Type 2) outpatient
Chronic heart disease
Cardiomyopathy
Coronary disease
Valvular disease
Chronic heart failure
Multiple risk factors (DM, HTN, *etc.*)
Increased oxidative stress
Endothelial dysfunction
Accelerated atherosclerotic and valvular calcification
Increased susceptibility to insults
Chronic hypo-perfusion
Apoptosis
Sclerosis-fibrosis
High CVP
Low cardiac output
Chronic hypo-perfusion
Increased renal vascular resistance
Increased venous pressure
Progression of CKD


Acute reno-cardiac syndrome (Type 3) hospitalized patient
Acute kidney injury
Glomerular disease
Interstitial disease
ATN
Acute pyelonephritis
Acute urinary obstruction
CI-AKI
CSA-AKI
Volume expansion
Hypertension
Sympathetic activation
RAAS-activation
Electrolyte, acid-base and coagulation imbalances
Labile iron release
Reactive oxygen species
Oxidative stress
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Acute heart dysfunction
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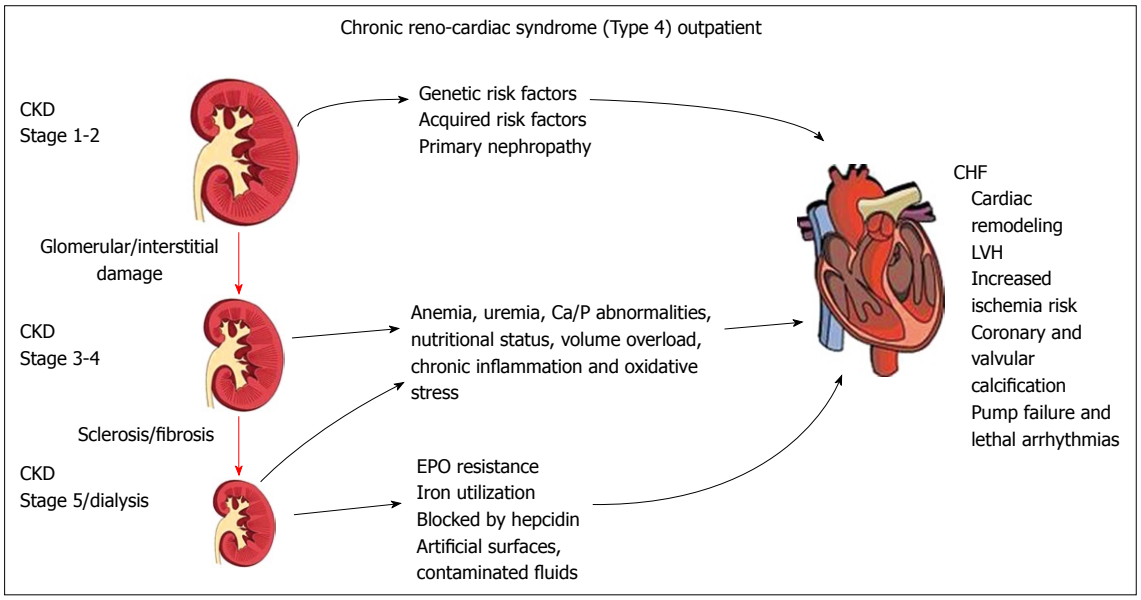
Arrhythmias
Low cardiac output


Chronic reno-cardiac syndrome (Type 4) outpatient
CKD
Stage 1-2
Genetic risk factors
Acquired risk factors
Primary nephropathy
Glomerular/interstitial damage
CKD
Stage 3-4
Anemia, uremia, Ca/P abnormalities, nutritional status, volume overload, chronic inflammation and oxidative stress
Sclerosis/fibrosis
CKD
Stage 5/dialysis
EPO resistance
Iron utilization
Blocked by hepcidin
Artificial surfaces, contaminated fluids
CHF
Cardiac remodeling
LVH
Increased ischemia risk
Coronary and valvular calcification
Pump failure and lethal arrhythmias

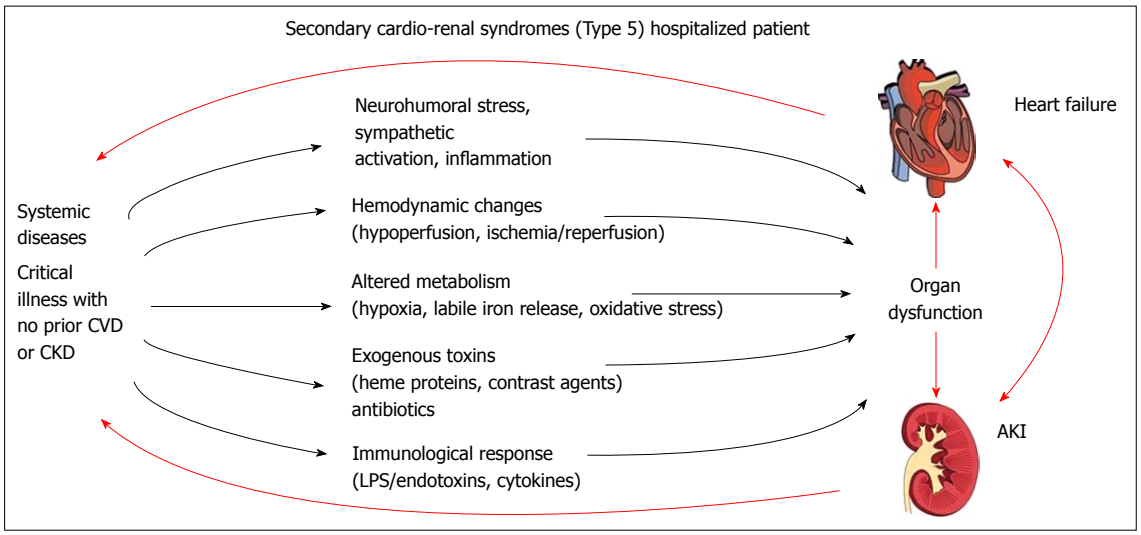


Figure 1 Pathophysiology and definitions of the five subtypes of cardiorenal syndromes. CVP: Central venous pressure; GFR: Glomerular filtration rate; BNP: Brain natriuretic peptide; ANP: Atrial natriuretic peptide; RAAS: Renin-angiotensin-aldosterone system ; ADHF: Acute decompensated heart failure; ACS: Acute coronary syndrome; CKD: Chronic kidney disease; CVD: Cardiovascular disease; ATN: Acute tubular necrosis; CI-AKI: Contrast-induced acute kidney injury; CSA-AKI: Cardiac surgery-associated AKI; CHF: Chronic heart failure; LVH: Left ventricular hypertrophy; EPO: Erythropoietin; LPS: Lipopolysaccharide.

revascularization for acute or chronic coronary disease. Acute contrast-induced and cardiopulmonary bypass surgery-associated AKI occur in 15% and 30% of patients, respectively[18,19]. Importantly, iodinated contrast which causes renal vasoconstriction and direct cellular toxicity to renal tubular cells is an important pre-existing factor in the few days before cardiac surgery. Cardiac surgery exposes the kidneys to hypothermic, pulseless reduced perfusion for 30-90 min, and thus represents a superimposed ischemic injury in the setting of a pro-inflammatory state[20]. It is possible that the extracorporeal circuit used in cardiopulmonary bypass surgery activates systemic factors that further induce AKI; however, attempts to limit this exposure have not resulted in significantly reduced rates of AKI[21]. Thus, these two scenarios are tightly linked, since almost every cardiac surgery patient operated upon in the urgent setting undergoes coronary angiography in the hours to days before surgery[22]. As with ADHF, CRS Type 1 in acute and chronic coronary disease has a confounded relationship with outcomes. In those with complications, CRS Type 1 appears to be independently associated with a 3 to 4-fold increase in mortality despite the availability of dialysis in the hospital[23,24]. In all forms of CRS Type 1, there is a risk of advancing to higher stages of CKD and ultimately the need for chronic renal replacement strategies[25]. The incremental and cumulative risk of these renal outcomes according to the clinical scenarios described above for an individual patient are unknown. Thus the important points concerning the epidemiology of CRS Type 1 are: (1) the mortality risk appears to be confounded by other non-renal complications occurring during the hospitalization; (2) intravascular iodinated contrast alone, and in cases where cardiac surgery follows coronary angiography, direct cellular toxicity from the contrast itself results in an observed rise in serum creatinine predominately in those with baseline reductions in renal filtration with additional risk factors, including diabetes, heart failure, older age, and larger contrast volumes; and (3) in the setting of ADHF, superimposed use of iodinated contrast or other cardiac procedures is associated with longer lengths of stay and higher mortality which is possibly in part, attributable to CRS Type 1[26-28].

Chronic cardiorenal syndrome

Chronic cardiorenal syndrome (CRS Type 2): chronic abnormalities in myocardial function leading to worsened chronic kidney disease (CKD). This subtype implies that chronic CVD can contribute to the development of CKD. Six observation studies have reported on CRS Type 2, with a minority of reports reporting on CVD contributing to an excess risk of CKD[4]. It is recognized that the risk factors for atherosclerosis, namely diabetes, hypertension, and smoking are independently associated with the development of CKD[29]. In addition, chronic abnormalities in systolic and diastolic myocardial performance can lead to alterations in neurohormonal activation, renal hemodynamics, and a variety of adverse cellular processes leading to apoptosis and renal fibrosis[30]. Approximately 30% of those with chronic cardiovascular disease (CVD) meet a definition of CKD, and multiple studies have demonstrated the independent contribution of CVD to the worsening of CKD[31]. An important component of CRS Type 2 epidemiology is that CKD appears to accelerate the course of atherosclerosis and result in premature CVD events including myocardial infarction and stroke[32,33]. Importantly, CKD and its metabolic milieu work to cause advanced calcific atherosclerosis through CKD mineral and bone disorder characterized by phosphate retention, relative vitamin D and calcium availability, and secondary hyperparathyroidism[34]. Of these factors, phosphate retention appears to be the critical pathophysiological component stimulating the conversion of vascular smooth

muscle cells to osteoblastic-like cells which, *via* the Pit-1 receptor, are stimulated to produce extracellular calcium hydroxyapatite crystals in the vascular smooth muscle layer of arteries[35,36]. Thus, patients as a part of CRS type 2, more commonly have vascular calcification, less vascular compliance, and a higher degree of chronic organ injury related to blood pressure elevation and shear stress[37]. Despite these mechanisms specific to CRS, CRS Type 2 remains heavily confounded by the "common soil" of atherosclerosis and CKD. The cardiometabolic syndrome and neurohormonal activation affect both organ systems; thus, it is difficult to tease out the temporal sequence of pathophysiological events for most individuals which are occurring over the period of decades[38].

Studies have shown that 45.0%-63.6% of patients with chronic HF have evidence of CKD defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min per 1.73 m^2[39]. Multiple studies have demonstrated that CKD is closely linked to more frequent hospitalizations and complications from pump failure and arrhythmias[40,41]. In addition, patients with CKD and end-stage renal disease have higher defibrillation thresholds and may not have the protective benefit of implantable cardio defibrillators as those with normal renal function[42]. Increased degrees of left ventricular hypertrophy and cardiac fibrosis are believed to be the biologic basis for these electrophysiological findings[43].

Acute renocardiac syndrome

Acute renocardiac syndrome (CRS Type 3): acute worsening of renal function leading to cardiac events. The most common scenario for CRS Type 3 is the development of AKI that results in volume overload, sodium retention, neurohormonal activation, and the development of clinical HF with the cardinal features of pulmonary congestion and peripheral edema. Volume overload alone has been shown to induce cardiac failure and reflect CRS Type 3 most clearly in the pediatric population[44]. However, in adults, when acute on chronic disease is a common occurrence, it is difficult to identify clear cases where AKI lead to cardiac decompensation. It is also possible that CRS Type 3 could precipitate in an acute coronary syndrome, stroke, or other acute cardiac event. Thus the epidemiology of this CRS subtype is not well defined for individual CVD events such as ACS, stroke, cardiac rehospitalization, arrhythmias, pump failure, and cardiac death[4].

Chronic renocardiac syndrome

Chronic renocardiac syndrome (CRS Type 4): chronic renal disease leading to the progression of cardiovascular disease. Over the past several decades there has been recognition of a graded and independent association between the severity of CKD and incidence as well as prevalence of CVD[2]. In a meta-analysis of 39 studies (1 371 990 participants), there was a clear relationship between the degree of renal dysfunction and the risk for all-cause mortality[45]. The unadjusted relative risk of mortality in participants with reduced kidney function was in excess of the reference group in 93% of cohorts. Fourteen of the 39 studies described the risk of mortality from reduced kidney function, after adjustment for other established risk factors. Although adjusted relative hazard ratios were on average 17% lower than unadjusted relative risks, they remained significantly greater than unity in 71% of cohorts. The overall mortality was influenced greatly by excess cardiovascular deaths, which constituted over 50% of cases. Thirteen studies have been identified as specifically reporting on CRS Type 4, most of which were in populations with end-stage renal disease[4]. It should also be recognized, that CKD contributes to CVD outcomes in CRS Type 4 by complicating pharmacological and interventional treatment[46,47]. For example, azotemia and hyperkalemia restrict the use of drugs that antagonize the renin-angiotensin system, thus fewer patients with CKD enjoy the cardiovascular benefits of angiotensin converting enzyme inhibitors, angiotensin Ⅱ receptor antagonists, and aldosterone receptor blockers[48,49]. It has been shown that CKD also worsens the presentation, severity, response to treatment, and cardiorenal outcomes in acute and chronic hypertension[50,51]. In addition, the perceived risks of AKI lead patients with CKD towards conservative management strategies which have been associated with poor outcomes in the setting of both acute and chronic coronary artery disease[52]. Finally, a recent study of silent brain injury (asymptomatic cerebral infarctions by magnetic resonance imaging) has been associated with a rapid decline in renal function in approximately 30% of patients[53]. This suggests the possibility that cerebrovascular disease could in some way contribute to more rapid progression of CKD.

Secondary cardiorenal syndrome

Secondary cardiorenal syndrome (CRS Type 5): systemic illness leading to simultaneous heart and renal failure. It is recognized that a systemic insult, particularly in a younger patient with no prior heart or kidney disease, can lead to simultaneous organ dysfunction. This is almost always in the setting of critical illness such as sepsis, multiple trauma, or burns. There are limited data on the incidence and determinants of CRS Type 5, in part because of confounders such as hypotension, respiratory failure, liver failure, and other organ injury beyond the cardiac and renal systems. This results in a difficult human model for investigation. Sepsis as a precipitator of CRS Type 5 is common and its incidence is increasing, with a mortality estimated at 20%-60%[54,55]. Approximately 11%-64% of septic patients develop AKI that is associated with a higher morbidity and mortality[56]. Abnormalities in cardiac function are also common in sepsis including wall motion abnormalities and transient reductions in left ventricular ejection fraction[57]. Observational data have found approximately 30%-80% of individuals with sepsis have measurable blood troponin I or T that are above the 99th detection limits[58]. These elevated cardiac biomarkers have been associated with reduced left ventricular function and higher mortality even in patients without known coronary

Table 1 Novel biomarkers of acute cardiac and renal injury

Biomarker	Mechanism of action	Advantages	Diagnostic approach	Potential therapeutic approaches
Catalytic (labile, poorly-liganded) iron	Leads to generation of the hydroxyl radical, the most destructive of ROS; released into the blood in patients with ACS[63]; thought to be involved in oxidative organ damage also in AKI[64]; local cellular and tissue availability of catalytic iron are likely to determine the degree and severity of organ injury in the setting of most hypoxic and other toxic insults[65]	In patients with ACS, the appearance of catalytic iron precedes the rise in serum troponin and detects acute myocardial infarction with an area under the ROC curve of > 90%[63]	Detection of non-transferrin-bound iron in blood by the bleomycin assay[63]	Use of iron chelators to diminish oxidative injury[66]
NGAL (lipocalin-2, siderocalin)	Natural siderophore produced by renal tubular cells that reduces the availability of catalytic iron, thus limiting oxidative damage and limiting bacterial growth	One of the earliest kidney markers of cardiac and renal injury in animals[65]; detected in humans shortly after AKI and predicts need for in-hospital dialysis[66]	Detection in blood and urine[67]	Overexpression reduces oxidative stress in ischemic injury[67]
Cystatin C	Cysteine protease inhibitor (housekeeping protein) produced by all nucleated cells that is freely filtered by the glomerulus and reabsorbed in the proximal tubule; no tubular secretion	Not dependent on muscle mass; better predictor of risk of adverse events in patients with CVD than creatinine or eGFR[68]	Detection in blood	-
KIM-1	Transmembrane glycoprotein not normally detected in urine[69]; detected in urine early after ischemic or nephrotoxic injury to cells of the proximal tubule[69]	Highly specific for AKI caused by systemic illnesses such as sepsis and not for pre-renal azotemia or drug-induced renal injury[68]; May be elevated before histologic evidence of proximal tubular cell death[69]	Detection in urine	-
NAG	Large lysosomal brush-border enzyme found in cells of the proximal tubule, not normally filtered by the glomerulus; elevated concentrations found in urine in the setting of AKI, CKD, diabetes mellitus, hypertension and heart failure[71]	Marker of the degree of tubular damage	Detection in urine	-
IL-18	Pro-inflammatory cytokine found in urine after acute ischemic damage to proximal tubules[72]; associated with AKI-related mortality, although not organ-specific[69]; might be involved in myocardial cell damage in the setting of ACS[73]	Sensitive and specific to detect ischemic AKI with an area under the ROC curve of 0.78[70]; levels rise 48 h before those of creatinine[68]	Detection in urine	Inhibitors expressed in stem cells are protective in models of myocyte injury[73]
L-FABP	Selectively binds free unsaturated fatty acids and products of lipid oxidation in cells in the setting of hypoxic tissue injury; detected in the urine in the setting of AKI[74]	Might predict dialysis-free survival in patients with AKI[75]	Detection in urine	-
Tubular enzymuria	Several enzymes, such as gamma glutamyl transpeptidase, alkaline phosphatase, lactate dehydrogenase, and α and π glutathione S-transferases are released from tubular cells[76-78]	A combination of measures of enzyme levels could potential indicate the presence and location of kidney injury[79]	Detection in urine	-

eGFR: Estimated glomerular filtration rate; KIM-1: Kidney injury molecule 1; IL-18: Interleukin-18; L-FABP: Liver-fatty acid binding protein; NAG: N-acetyl-β-(D)glucosaminidase; NGAL: Neutrophil gelatinase-associated lipocalin; ROC: Receiver operating characteristic; ROS: Reactive oxygen species.

disease[59-61]. Importantly, volume overload as a result of aggressive fluid resuscitation appears to be a significant determinant of CRS Type 5. Among 3147 patients enrolled in the Sepsis Occurrence in Acutely Ill Patients (SOAP), there was a 36% incidence of AKI, and volume overload was the strongest predictor of mortality[59]. Iatrogenic volume overload appears to play an important additional role, possibly along the lines described for CRS Type 1 and passive venous congestion of the kidney, in the pathogenesis of AKI. At the same time, volume overload increases left ventricular wall tension and likely contributes to cardiac decompensation in those predisposed to both systolic and diastolic HF[60]. In summary for CRS Type 5, both AKI and markers of cardiac injury followed by volume overload are common in sepsis, with each being associated with increased mortality. However, there is a current lack of integral information on the incidence of bidirectional organ failure and its pathophysiological correlates in a variety of acute care settings.

BIOMARKERS OF CARDIORENAL SYNDROMES

There is considerable interest in blood and urine biomarkers to detect CRS. For decades, the rise in serum creatinine has been the only detectable sign of a reduction in glomerular filtration. Creatinine has had the disadvantages of being linked to creatine and overall body muscle mass, hence varying according to body size in addition to the rate of renal elimination[61]. Furthermore, the kidney both filters and secretes creatinine. Finally, the assays used to measure creatinine have not be standardized across laboratories, therefore studies reporting values from multiple centers have inherent variation in values attributed to dif-

ferences in measurement technique[62]. Hence, there is a clear need for better laboratory markers of renal filtration. An ideal marker would be independent of muscle mass, reflect actual renal filtration at the time of measurement, and be sensitive to changes in actual GFR in order to alert clinicians to a meaningful change shortly after it occurs.

Unlike cardiac biomarkers indicating myocardial injury and overload (troponin, creatine kinase myocardial band, natriuretic peptides), the field of nephrology has been devoid of approved blood or urine markers of AKI. Thus the current paradigm is that when renal injury occurs, clinicians must wait to observe a reduction in GFR before AKI is inferred. The concept of measuring markers of the acute injury process is crucial to the early upstream identification of AKI before there is serious loss of organ function[63]. Table 1 is a summary of relatively novel renal markers and what is known about them in acute cardiac and renal injury. Their use in the years to come will undoubtedly influence the epidemiology of CRS.

IMPACT ON HOSPITAL MEDICINE

Cardiorenal syndromes as described in this paper are not spontaneous or primary conditions that arise in free-living populations. Acute CRS appears to occur once hospitalization and its associated care have occurred. Thus, there are determinants and clear precipitants to these syndromes that are potentially controllable by clinicians. Improved education and awareness concerning the risk factors and presence of CKD holds great promise for patients and clinicians to avoid contributors to CRS such as excess sodium intake, and use of intensive loop diuretics, nonsteroidal anti-inflammatory agents, thiazolidinediones, and iodinated contrast. The National Kidney Foundation Kidney Early Evaluation Program is a nationwide and now global community-based screening program that evaluates volunteers for CKD and its risk factors, with effective education for participants and their physicians[64]. This program, as it evolves and broadens, has a considerable opportunity to lessen the frequency of avoidable CRS in the future by spurring community awareness and clinical appreciation for CKD. Finally, the most important public health question concerning this field is wether or not a lessening of the frequency or severity of AKI will reduce hospital length of stay, cardiovascular, renal, and all-cause morbidity and mortality. Large scale clinical trials of preventive therapies that consign broad composite primary endpoints with biomarkers as secondary endpoints are needed to answer this pivotal question.

CONCLUSION

The ADQI consensus on CRS has yielded a framework for a better understanding of the epidemiology of the five subtypes of CRS[3]. A description of the epidemiology of the heart-kidney interaction is critical to our understanding of the overall disease burden associated with these specific CRS subtypes, and will guide future investigations into their pathophysiology, diagnosis, prognosis, and management. Recent studies have identified and characterized several novel biomarkers for HF and AKI. These advances will herald better understanding, diagnosis, and treatment of CRS. It is anticipated that these biomarkers will help make an earlier diagnosis of CRS possible, as well as identify the specific type of CRS. It is hoped that some of these new biomarkers will either provide sufficient risk prediction or early diagnosis of all patients for novel preventive and treatment strategies to ameliorate the course of CRS, and subsequently, the long-term outcome.

REFERENCES

1 **McCullough PA**. Why is chronic kidney disease the "spoiler" for cardiovascular outcomes? *J Am Coll Cardiol* 2003; **41**: 725-728

2 **Sarnak MJ**, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Circulation* 2003; **108**: 2154-2169

3 **Ronco C**, McCullough P, Anker SD, Anand I, Aspromonte N, Bagshaw SM, Bellomo R, Berl T, Bobek I, Cruz DN, Daliento L, Davenport A, Haapio M, Hillege H, House AA, Katz N, Maisel A, Mankad S, Zanco P, Mebazaa A, Palazzuoli A, Ronco F, Shaw A, Sheinfeld G, Soni S, Vescovo G, Zamperetti N, Ponikowski P. Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. *Eur Heart J* 2010; **31**: 703-711

4 **Shah SV**. Oxidants and iron in chronic kidney disease. *Kidney Int Suppl* 2004; S50-S55

5 **Walker BL**, Tiong JW, Jefferies WA. Iron metabolism in mammalian cells. *Int Rev Cytol* 2001; **211**: 241-278

6 **Richardson DR**, Lane DJ, Becker EM, Huang ML, Whitnall M, Rahmanto YS, Sheftel AD, Ponka P. Mitochondrial iron trafficking and the integration of iron metabolism between the mitochondrion and cytosol. *Proc Natl Acad Sci USA* 2010; **107**: 10775-10782

7 **Balla J**, Vercellotti GM, Jeney V, Yachie A, Varga Z, Jacob HS, Eaton JW, Balla G. Heme, heme oxygenase, and ferritin: how the vascular endothelium survives (and dies) in an iron-rich environment. *Antioxid Redox Signal* 2007; **9**: 2119-2137

8 **Jelani QU**, Katz SD. Treatment of anemia in heart failure: potential risks and benefits of intravenous iron therapy in cardiovascular disease. *Cardiol Rev* 2010; **18**: 240-250

9 **Rooyakkers TM**, Stroes ES, Kooistra MP, van Faassen EE, Hider RC, Rabelink TJ, Marx JJ. Ferric saccharate induces oxygen radical stress and endothelial dysfunction in vivo. *Eur J Clin Invest* 2002; **32** Suppl 1: 9-16

10 **Kooistra MP**, Kersting S, Gosriwatana I, Lu S, Nijhoff-Schutte J, Hider RC, Marx JJ. Nontransferrin-bound iron in the plasma of haemodialysis patients after intravenous iron saccharate infusion. *Eur J Clin Invest* 2002; **32** Suppl 1: 36-41

11 **Zanen AL**, Adriaansen HJ, van Bommel EF, Posthuma R, Th de Jong GM. 'Oversaturation' of transferrin after intravenous ferric gluconate (Ferrlecit(R)) in haemodialysis patients. *Nephrol Dial Transplant* 1996; **11**: 820-824

12 **Bagshaw SM**, Cruz DN, Aspromonte N, Daliento L, Ronco F, Sheinfeld G, Anker SD, Anand I, Bellomo R, Berl T, Bobek I, Davenport A, Haapio M, Hillege H, House A, Katz N, Maisel A, Mankad S, McCullough P, Mebazaa A, Palazzuoli A, Ponikowski P, Shaw A, Soni S, Vescovo G, Zamperetti N, Zanco P, Ronco C. Epidemiology of cardio-renal syndromes: work-

group statements from the 7th ADQI Consensus Conference. *Nephrol Dial Transplant* 2010; **25**: 1406-1416
13 **Forman DE**, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlieb SS, Loh E, Massie BM, Rich MW, Stevenson LW, Young JB, Krumholz HM. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol* 2004; **43**: 61-67
14 **Cowie MR**, Komajda M, Murray-Thomas T, Underwood J, Ticho B. Prevalence and impact of worsening renal function in patients hospitalized with decompensated heart failure: results of the prospective outcomes study in heart failure (POSH). *Eur Heart J* 2006; **27**: 1216-1222
15 **Metra M**, Nodari S, Parrinello G, Bordonali T, Bugatti S, Danesi R, Fontanella B, Lombardi C, Milani P, Verzura G, Cotter G, Dittrich H, Massie BM, Dei Cas L. Worsening renal function in patients hospitalised for acute heart failure: clinical implications and prognostic significance. *Eur J Heart Fail* 2008; **10**: 188-195
16 **Testani JM**, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. *Circulation* 2010; **122**: 265-272
17 **Tang WH**, Mullens W. Cardiorenal syndrome in decompensated heart failure. *Heart* 2010; **96**: 255-260
18 **McCullough PA**. Contrast-induced acute kidney injury. *J Am Coll Cardiol* 2008; **51**: 1419-1428
19 **Bellomo R**, Auriemma S, Fabbri A, D'Onofrio A, Katz N, McCullough PA, Ricci Z, Shaw A, Ronco C. The pathophysiology of cardiac surgery-associated acute kidney injury (CSA-AKI). *Int J Artif Organs* 2008; **31**: 166-178
20 **Elahi MM**, Battula NR, Hakim NS, Matata BM. Acute renal failure in patients with ischemic heart disease: causes and novel approaches in breaking the cycle of self-perpetuating insults abrogated by surgery. *Int Surg* 2005; **90**: 202-208
21 **Diez C**, Haneya A, Brünger F, Philipp A, Hirt S, Ruppecht L, Kobuch R, Keyser A, Hilker M, Puehler T, Schmid C. Minimized extracorporeal circulation cannot prevent acute kidney injury but attenuates early renal dysfunction after coronary bypass grafting. *ASAIO J* 2009; **55**: 602-607
22 **Ranucci M**, Ballotta A, Kunkl A, De Benedetti D, Kandil H, Conti D, Mollichelli N, Bossone E, Mehta RH. Influence of the timing of cardiac catheterization and the amount of contrast media on acute renal failure after cardiac surgery. *Am J Cardiol* 2008; **101**: 1112-1118
23 **McCullough PA**, Wolyn R, Rocher LL, Levin RN, O'Neill WW. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med* 1997; **103**: 368-375
24 **Del Duca D**, Iqbal S, Rahme E, Goldberg P, de Varennes B. Renal failure after cardiac surgery: timing of cardiac catheterization and other perioperative risk factors. *Ann Thorac Surg* 2007; **84**: 1264-1271
25 **Newsome BB**, Warnock DG, McClellan WM, Herzog CA, Kiefe CI, Eggers PW, Allison JJ. Long-term risk of mortality and end-stage renal disease among the elderly after small increases in serum creatinine level during hospitalization for acute myocardial infarction. *Arch Intern Med* 2008; **168**: 609-616
26 **McCullough PA**, Stacul F, Becker CR, Adam A, Lameire N, Tumlin JA, Davidson CJ. Contrast-Induced Nephropathy (CIN) Consensus Working Panel: executive summary. *Rev Cardiovasc Med* 2006; **7**: 177-197
27 **Smith GL**, Lichtman JH, Bracken MB, Shlipak MG, Phillips CO, DiCapua P, Krumholz HM. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. *J Am Coll Cardiol* 2006; **47**: 1987-1996
28 **Philbin EF**, McCullough PA, Dec GW, DiSalvo TG. Length of stay and procedure utilization are the major determinants of hospital charges for heart failure. *Clin Cardiol* 2001; **24**: 56-62
29 **Kundhal K**, Lok CE. Clinical epidemiology of cardiovascular disease in chronic kidney disease. *Nephron Clin Pract* 2005; **101**: c47-c52
30 **Chinnaiyan KM**, Alexander D, McCullough PA. Role of angiotensin II in the evolution of diastolic heart failure. *J Clin Hypertens* (Greenwich) 2005; **7**: 740-747
31 **McCullough PA**, Jurkovitz CT, Pergola PE, McGill JB, Brown WW, Collins AJ, Chen SC, Li S, Singh A, Norris KC, Klag MJ, Bakris GL. Independent components of chronic kidney disease as a cardiovascular risk state: results from the Kidney Early Evaluation Program (KEEP). *Arch Intern Med* 2007; **167**: 1122-1129
32 **Yerkey MW**, Kernis SJ, Franklin BA, Sandberg KR, McCullough PA. Renal dysfunction and acceleration of coronary disease. *Heart* 2004; **90**: 961-966
33 **McCullough PA**, Li S, Jurkovitz CT, Stevens L, Collins AJ, Chen SC, Norris KC, McFarlane S, Johnson B, Shlipak MG, Obialo CI, Brown WW, Vassalotti J, Whaley-Connell AT, Brenner RM, Bakris GL. Chronic kidney disease, prevalence of premature cardiovascular disease, and relationship to short-term mortality. *Am Heart J* 2008; **156**: 277-283
34 **McCullough PA**, Sandberg KR, Dumler F, Yanez JE. Determinants of coronary vascular calcification in patients with chronic kidney disease and end-stage renal disease: a systematic review. *J Nephrol* 2004; **17**: 205-215
35 **Tintut Y**, Demer LL. Recent advances in multifactorial regulation of vascular calcification. *Curr Opin Lipidol* 2001; **12**: 555-560
36 **McCullough PA**, Agrawal V, Danielewicz E, Abela GS. Accelerated atherosclerotic calcification and Monckeberg's sclerosis: a continuum of advanced vascular pathology in chronic kidney disease. *Clin J Am Soc Nephrol* 2008; **3**: 1585-1598
37 **Guérin AP**, Pannier B, Métivier F, Marchais SJ, London GM. Assessment and significance of arterial stiffness in patients with chronic kidney disease. *Curr Opin Nephrol Hypertens* 2008; **17**: 635-641
38 **Bays HE**. "Sick fat," metabolic disease, and atherosclerosis. *Am J Med* 2009; **122**: S26-S37
39 **Ahmed A**, Rich MW, Sanders PW, Perry GJ, Bakris GL, Zile MR, Love TE, Aban IB, Shlipak MG. Chronic kidney disease associated mortality in diastolic versus systolic heart failure: a propensity matched study. *Am J Cardiol* 2007; **99**: 393-398
40 **Soman SS**, Sandberg KR, Borzak S, Hudson MP, Yee J, McCullough PA. The independent association of renal dysfunction and arrhythmias in critically ill patients. *Chest* 2002; **122**: 669-677
41 **Jenkins K**, Kirk M. Heart failure and chronic kidney disease: an integrated care approach. *J Ren Care* 2010; **36** Suppl 1: 127-135
42 **Wase A**, Basit A, Nazir R, Jamal A, Shah S, Khan T, Mohiuddin I, White C, Saklayen M, McCullough PA. Impact of chronic kidney disease upon survival among implantable cardioverter-defibrillator recipients. *J Interv Card Electrophysiol* 2004; **11**: 199-204
43 **Glassock RJ**, Pecoits-Filho R, Barberato SH. Left ventricular mass in chronic kidney disease and ESRD. *Clin J Am Soc Nephrol* 2009; **4** Suppl 1: S79-S91
44 **Bagshaw SM**, Cruz DN. Fluid overload as a biomarker of heart failure and acute kidney injury. *Contrib Nephrol* 2010; **164**: 54-68
45 **Tonelli M**, Wiebe N, Culleton B, House A, Rabbat C, Fok M, McAlister F, Garg AX. Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol* 2006; **17**: 2034-2047
46 **Shlipak MG**. Pharmacotherapy for heart failure in patients with renal insufficiency. *Ann Intern Med* 2003; **138**: 917-924
47 **McCullough PA**, Berman AD. Percutaneous coronary interventions in the high-risk renal patient: strategies for renal protection and vascular protection. *Cardiol Clin* 2005; **23**: 299-310
48 **McCullough PA**, Sandberg KR, Yee J, Hudson MP. Mortality benefit of angiotensin-converting enzyme inhibitors after car-

diac events in patients with end-stage renal disease. *J Renin Angiotensin Aldosterone Syst* 2002; **3**: 188-191
49 **McCullough PA**. Chronic kidney disease: tipping the scale to the benefit of angiotensin-converting enzyme inhibitors in patients with coronary artery disease. *Circulation* 2006; **114**: 6-7
50 **Kalaitzidis R**, Li S, Wang C, Chen SC, McCullough PA, Bakris GL. Hypertension in early-stage kidney disease: an update from the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis* 2009; **53**: S22-S31
51 **Szczech LA**, Granger CB, Dasta JF, Amin A, Peacock WF, McCullough PA, Devlin JW, Weir MR, Katz JN, Anderson FA Jr, Wyman A, Varon J. Acute kidney injury and cardiovascular outcomes in acute severe hypertension. *Circulation* 2010; **121**: 2183-2191
52 **Keeley EC**, Kadakia R, Soman S, Borzak S, McCullough PA. Analysis of long-term survival after revascularization in patients with chronic kidney disease presenting with acute coronary syndromes. *Am J Cardiol* 2003; **92**: 509-514
53 **Kobayashi M**, Hirawa N, Morita S, Yatsu K, Kobayashi Y, Yamamoto Y, Saka S, Toya Y, Yasuda G, Umemura S. Silent brain infarction and rapid decline of kidney function in patients with CKD: a prospective cohort study. *Am J Kidney Dis* 2010; **56**: 468-476
54 **Angus DC**, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001; **29**: 1303-1310
55 **Martin GS**, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med* 2003; **348**: 1546-1554
56 **Bagshaw SM**, Lapinsky S, Dial S, Arabi Y, Dodek P, Wood G, Ellis P, Guzman J, Marshall J, Parrillo JE, Skrobik Y, Kumar A. Acute kidney injury in septic shock: clinical outcomes and impact of duration of hypotension prior to initiation of antimicrobial therapy. *Intensive Care Med* 2009; **35**: 871-881
57 **Lopes JA**, Jorge S, Resina C, Santos C, Pereira A, Neves J, Antunes F, Prata MM. Acute renal failure in patients with sepsis. *Crit Care* 2007; **11**: 411
58 **Zanotti-Cavazzoni SL**, Hollenberg SM. Cardiac dysfunction in severe sepsis and septic shock. *Curr Opin Crit Care* 2009; **15**: 392-397
59 **Favory R**, Neviere R. Significance and interpretation of elevated troponin in septic patients. *Crit Care* 2006; **10**: 224
60 **Ammann P**, Maggiorini M, Bertel O, Haenseler E, Joller-Jemelka HI, Oechslin E, Minder EI, Rickli H, Fehr T. Troponin as a risk factor for mortality in critically ill patients without acute coronary syndromes. *J Am Coll Cardiol* 2003; **41**: 2004-2009
61 **Mehta NJ**, Khan IA, Gupta V, Jani K, Gowda RM, Smith PR. Cardiac troponin I predicts myocardial dysfunction and adverse outcome in septic shock. *Int J Cardiol* 2004; **95**: 13-17
62 **Vincent JL**, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, Moreno R, Carlet J, Le Gall JR, Payen D. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med* 2006; **34**: 344-353
63 **Chinnaiyan KM**, Alexander D, Maddens M, McCullough PA. Curriculum in cardiology: integrated diagnosis and management of diastolic heart failure. *Am Heart J* 2007; **153**: 189-200
64 **Myers GL**, Miller WG, Coresh J, Fleming J, Greenberg N, Greene T, Hostetter T, Levey AS, Panteghini M, Welch M, Eckfeldt JH. Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. *Clin Chem* 2006; **52**: 5-18
65 **Stevens LA**, Stoycheff N. Standardization of serum creatinine and estimated GFR in the Kidney Early Evaluation Program (KEEP). *Am J Kidney Dis* 2008; **51**: S77-S82
66 **Soni SS**, Ronco C, Katz N, Cruz DN. Early diagnosis of acute kidney injury: the promise of novel biomarkers. *Blood Purif* 2009; **28**: 165-174
67 **McCullough PA**, Vassalotti JA, Collins AJ, Chen SC, Bakris GL. National Kidney Foundation's Kidney Early Evaluation Program (KEEP) annual data report 2009: executive summary. *Am J Kidney Dis* 2010; **55**: S1-S3
68 **Mishra J**, Ma Q, Prada A, Mitsnefes M, Zahedi K, Yang J, Barasch J, Devarajan P. Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. *J Am Soc Nephrol* 2003; **14**: 2534-2543
69 **Nickolas TL**, O'Rourke MJ, Yang J, Sise ME, Canetta PA, Barasch N, Buchen C, Khan F, Mori K, Giglio J, Devarajan P, Barasch J. Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. *Ann Intern Med* 2008; **148**: 810-819
70 **Mori K**, Lee HT, Rapoport D, Drexler IR, Foster K, Yang J, Schmidt-Ott KM, Chen X, Li JY, Weiss S, Mishra J, Cheema FH, Markowitz G, Suganami T, Sawai K, Mukoyama M, Kunis C, D'Agati V, Devarajan P, Barasch J. Endocytic delivery of lipocalin-siderophore-iron complex rescues the kidney from ischemia-reperfusion injury. *J Clin Invest* 2005; **115**: 610-621
71 **Parikh CR**, Devarajan P. New biomarkers of acute kidney injury. *Crit Care Med* 2008; **36**: S159-S165
72 **Edelstein CL**. Biomarkers of acute kidney injury. *Adv Chronic Kidney Dis* 2008; **15**: 222-234
73 **Liangos O**, Tighiouart H, Perianayagam MC, Kolyada A, Han WK, Wald R, Bonventre JV, Jaber BL. Comparative analysis of urinary biomarkers for early detection of acute kidney injury following cardiopulmonary bypass. *Biomarkers* 2009; **14**: 423-431
74 **Portilla D**, Dent C, Sugaya T, Nagothu KK, Kundi I, Moore P, Noiri E, Devarajan P. Liver fatty acid-binding protein as a biomarker of acute kidney injury after cardiac surgery. *Kidney Int* 2008; **73**: 465-472
75 **Ferguson MA**, Vaidya VS, Waikar SS, Collings FB, Sunderland KE, Gioules CJ, Bonventre JV. Urinary liver-type fatty acid-binding protein predicts adverse outcomes in acute kidney injury. *Kidney Int* 2010; **77**: 708-714
76 **McMahon BA**, Koyner JL, Murray PT. Urinary glutathione S-transferases in the pathogenesis and diagnostic evaluation of acute kidney injury following cardiac surgery: a critical review. *Curr Opin Crit Care* 2010; Epub ahead of print
77 **Branten AJ**, Mulder TP, Peters WH, Assmann KJ, Wetzels JF. Urinary excretion of glutathione S transferases alpha and pi in patients with proteinuria: reflection of the site of tubular injury. *Nephron* 2000; **85**: 120-126
78 **Walshe CM**, Odejayi F, Ng S, Marsh B. Urinary glutathione S-transferase as an early marker for renal dysfunction in patients admitted to intensive care with sepsis. *Crit Care Resusc* 2009; **11**: 204-209
79 **Westhuyzen J**, Endre ZH, Reece G, Reith DM, Saltissi D, Morgan TJ. Measurement of tubular enzymuria facilitates early detection of acute renal impairment in the intensive care unit. *Nephrol Dial Transplant* 2003; **18**: 543-551

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EDITORIAL

Hemodynamic assessment of pulmonary hypertension

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Abstract

There has been significant progress in our understanding of the pathobiology, epidemiology and prognosis of pulmonary vascular disease and, over the past few years, there has been an explosion of clinical therapeutic trials for pulmonary arterial hypertension (PAH). The increasing number of different conditions now associated with PAH and the appearance of new diagnostic techniques have led to a need for a systematic diagnostic approaches and a new disease classification, which has resulted in notable improvements in the quality and efficacy of clinical care. We appreciate traditional resting right heart catheterization techniques (which still remain the gold standard for diagnosing PAH and managing patients on therapy) and look forward to novel invasive techniques (e.g. intravascular ultrasound) that add greatly to our understanding of right ventricle and pulmonary circulation, and for the interpretation of data from clinical trials as well.

Key words: Pulmonary hypertension; Right heart catheterization; Intravascular ultrasound; Pulmonary artery stiffness

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INTRODUCTION

We have experienced significant progress in our understanding of pulmonary hypertension (PH) including elucidation of the pathobiology of PH and the development of diagnostic approaches, treatments and prognostic abilities[1]. Many cardiac and pulmonary diseases are associated with an abnormal increase in pulmonary artery pressures (PAP). The most common causes of PH are left heart failure and chronic hypoxemic lung diseases. PH is the third most common cardiovascular condition, after coronary heart disease and systemic hypertension. A resting mean PAP (mPAP) of 8 to 20 mmHg should be considered normal, based on available evidence. According to the last World Symposium on PH held in DanaPoint (2008), PH is a hemodynamic and pathophysiological condition defined as an increase in mPAP $\geqslant$ 25 mmHg at rest as assessed by right heart catheterization (RHC, Table 1). Further studies are needed to better determine the natural history of patients with mPAP of 21 to 24 mmHg. Currently, the normal behavior of pulmonary pressure during exercise remains unknown, and it presents wide variability according to age and the degree of physical fitness in the healthy individuals. Thus, a definition of PH during exercise as a mPAP > 30 mmHg is not supported by published data. PH can be found in multiple clinical conditions, which have been classified into 6 clinical groups with different pathological, pathophysiological, prognostic and therapeutic features[1].

The subgroup of PH known as pulmonary arterial hypertension (PAH, group 1) is a clinical condition characterized by the presence of precapillary PH (pulmonary arterial wedge pressure ⩽ 15 mmHg) in the absence of other causes of precapillary PH, such as PH due to lung diseases, chronic thromboembolic PH or other rare diseases.

PH is a life threatening disease characterized by a progressive increase of pulmonary blood pressure that often leads to right ventricular (RV) failure and death. In fact, PAH is a disease of the arterial vessel wall (obliterative proliferation and remodelling) that affects both steady and pulsatile components of the pulmonary arterial hemodynamics. The increase of the pulmonary vascular resistance (PVR), the intrinsic wall arterial stiffness and the magnitude and timing of the reflection wave (secondary to the increase pulse wave velocity), determine a progressive dynamic afterload increase, which in turn leads to RV hypertrophy, dilatation and failure[2].

The maintenance of stroke volume or ventricular flow output in the presence of an increase of the afterload depends on systolic function adaptation, with secondary diastolic changes and altered RV-left ventricle (LV) interactions. The insufficient homeometric adaptation to afterload (Anrep effect) leads to heterometric adaptation (Starling effect), given the increased preload is secondary to the RV dilatation. Finally, the exhaustion of these mechanisms plus the ventricular contractility decrease, extended relaxation time constant and increased stiffness, determines RV failure[3].

Taking into account that RV functional status is a strong predictor of survival and that the evolution of RV function parallels the evolution of the pulmonary vascular anatomo-functional pathology, it is becoming apparent that a comprehensive approach to the RV, pulmonary circulation and their interactions as a unit (ventricular-pulmonary vascular coupling) will be beneficial in both clinical management of PH patients and clinical research. Here we discuss standard and evolving invasive parameters that have the ability to better assess pulmonary circulation and RV function as a unit[2].

STANDARD INVASIVE HEMODYNAMIC PARAMETERS

Right heart catheterization (RHC) remains the gold standard for diagnosing PH, assessing disease severity, and determining the prognosis and response to therapy (Table 2)[4]. The procedure has been shown to be safe, with no deaths reported in the NIH registry study. In addition, a recent study reported a procedure-related mortality of 0.055% and morbidity of 1.1% when conducted in specialized centers. The most critical aspects of RHC are that it is performed appropriately and the data are interpreted accurately. Since end-expiratory intrathoracic pressure most closely correlates with atmospheric pressure, it is important that all RV, pulmonary artery (PA), PA occlusion pressure (PAOP), and left ventricular pressures be measured at end-expiration (specially in obese patients and patients with intrinsic lung disease in whom there can be significant variation between inspiration and end-expiratory vascular pressures)[2-5].

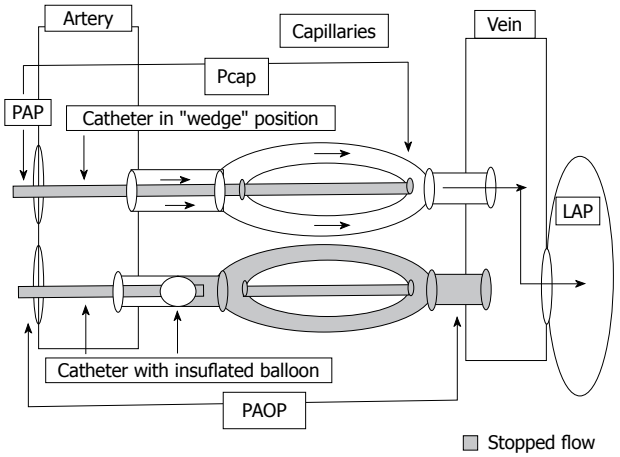

Figure 1 Occluded pulmonary artery pressure *vs* pulmonary capillary wedge pressure. Modified from Lupi Herrera *et al*. Arch Cardiol Mex 2008; 78: 95-113.

After determination of the presence of PH, pulmonary venous pressure should be evaluated by the PAOP. Inflation of the balloon at the tip of a PA catheter to measure PAOP creates a downstream stop-flow phenomenon extending to the same diameter veins. Therefore, PAOP generally gives a satisfactory estimate of left atrial (LA) or end-diastolic LV pressure (Figure 1)[6]. In order to obtain retrograde transmission of LA events through the pulmonary capillary bed (i.e. PAOP), the PA catheter tip must be located in a lung segment where pulmonary venous pressure exceeds the alveolar pressure (physiologic zone 3). Conditions such as hypovolemia, advanced parenchymal lung disease, or positive pressure ventilation make the alveolar pressure exceed the pulmonary venous pressure, therefore creating zones 1 or 2. In this case, PAOP becomes a measure of alveolar pressure rather than LA pressure[7].

Because the PAOP is a backward reflection of the LA, the timing of the waves with the ECG is slightly delayed: the *a* wave occurs with atrial contraction and is found near the end or after the QRS and the *v* wave occurs when blood fills the atria and the mitral valve is closed. This is observed well after the T wave. A very prominent v wave can hinder the accurate measurement of PAOP and tends to appear due to severe mitral regurgitation or severe alterations in LV distensibility[6,7].

To measure the mean PAOP value, we must locate the *a* wave (near or after the QRS complex) and measure the maximum and minimum a wave values, and then these values are averaged (Figure 2).

Wedging a PA catheter without balloon inflation yields a PA wedge pressure, sometimes called a pulmonary capillary wedge pressure (Pcwp) or (wrongly) a pulmonary capillary pressure (Pcap), which measures the pressure of the same diameter veins (Figure 1). The

Table 1 Hemodynamic definitions of pulmonary hypertension as assessed by right heart catheterization

Definition	Characteristics	Clinical group(s)[1]
PH	mPAP ⩾ 25 mmHg	All
Pre-capillary PH	mPAP ⩾ 25 mmHg	1 Pulmonary arterial hypertension
	PAOP ⩽ 15 mmHg	3 PH due to lung diseases
	CO N or reduced[2]	4 Chronic thromboembolic PH
		5 PH with unclear and/or multi- factorial mechanisms
Post-capillary PH	mPAP ⩾ 25 mmHg	2 PH due to left heart disease
	PAOP > 15 mmHg	
	CO N or reduced[2]	
Passive	TPG ⩽ 12 mmHg	
Reactive ("out of proportion")	TPG > 12 mmHg	

[1]DanaPoint classification; [2]High cardiac output can be present in cases of hyperkinetic conditions such as systemic-to-pulmonary shunts (only in the pulmonary circulation), anemia, hyperthyroidism, *etc.* PH: Pulmonary hypertension; CO: Cardiac output; PAP: Pulmonary arterial pressure; PAOP: Pulmonary artery occlusion pressure; TPG: Transpulmonary pressure gradient (mPAP-PAOP).

Table 2 Recommendations for right heart catheterization[1]

Statement	Class of re-commendation	Level of evidence
RHC is indicated in all patients with pulmonary arterial hypertension to confirm the diagnosis, to evaluate the severity and when PAH specific drug is considered	I	C
RHC should be performed for confirmation of efficacy of pulmonary arterial hypertension specific drug therapy	IIa	C
RHC should be performed for confirmation of clinical deterioration and as baseline for the evaluation of the effect of treatment escalation and/or combination therapy	IIa	C

RHC: Right heart catheterization.

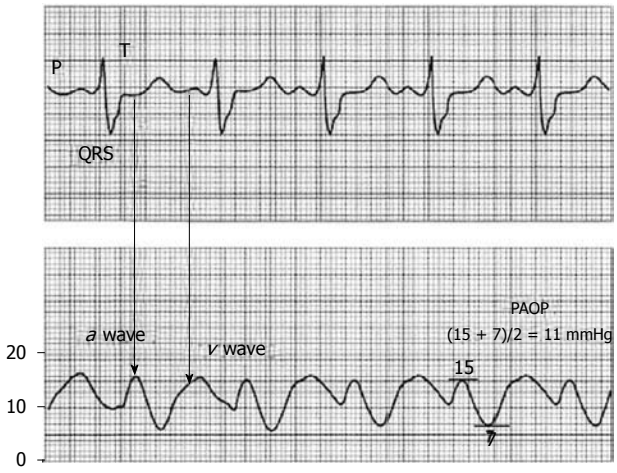

Figura 2 Timing of the pulmonary artery occlusion pressure waves. PACEP program, http://www.pacep.org.

measurement of an effective Pcap, requires the analysis of a PAP decay curve after balloon occlusion, as will be described later[8,9].

A hemodynamic study was recently conducted in 3920 patients with PH, and the reliability of PAOP to distinguish PAH and PH associated with LV disease compared to LV end-diastolic pressure (the gold standard of LV preload) was analyzed. Approximately half of the patients classified as having PAH based on PAOP < 15 mmHg, actually had PH associated with LV disease when based on the criterion of an LV end-diastolic pressure < 15 mmHg. Thus, if the patient presents a clinical profile compatible with PH associated with LV disease (age > 65 years, obesity, metabolic syndrome, coronary artery disease, hypertension, diabetes mellitus, LA enlargement, LV hypertrophy), a direct measurement of LV end-diastolic pressure is recommended to confirm the diagnosis of PAH if PAOP is < 15 mmHg[10].

The normal value of PAOP or LV end diastolic pressure is less than 8 mmHg and no more than 15 mmHg, since approximately 14 mmHg is 2 standard deviations from a normal PAOP. In clinical practice, Pcap is seldom assessed, and PAOP (confusingly called Pcwp or Pcap) is commonly used to estimate PVR and to guide fluid therapy. Under numerous pathological conditions the longitudinal distribution of the precapillary arterial and the postcapillary venous resistance and subsequently the relationship between Pcap and PAOP varies greatly. Hence, Pcap can no longer be predicted from PAOP. The measurement of the effective Pcap requires the analysis of a PAOP decay curve after balloon occlusion through different methods: (1) the visual inspection method, where the inflection point is designated as the capillary pressure; (2) a single exponential curve is fitted to the average arterial occlusion pressure decay in the segment between 0.3 s and 2 s after time 0 (occlusion); and (3) a better fit of PAOP decay curves after balloon occlusion is obtained with a bi-exponential function. This method of calculation led to lower Pcap values than found using a mono-exponential fitting (Figure 3)[6,8,11].

When the PA is occluded, there is a rapid decrease in

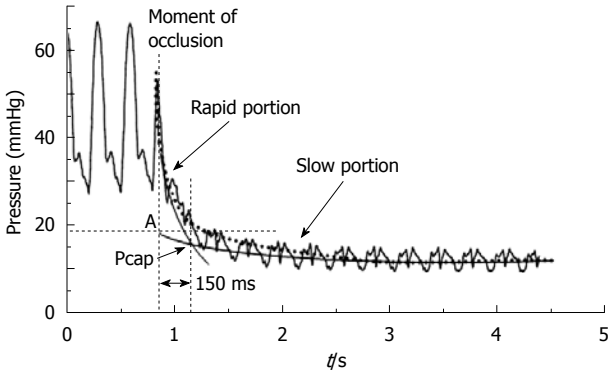

Figure 3 Biexponential curve fitting for estimation of pulmonary capillary pressure (Pcap) by intersection of the fast and the slow components of the pressure decay curve, or by the extrapolation of the exponential fitting of the slow component of the pressure decay curve to the moment of occlusion. Modified from Souza *et al*. Critical Care 2005, 9: R132-R138.

blood flow as the occluded downstream PA discharges its blood volume sequentially into the pulmonary capillaries across the arterial resistance and then into the pulmonary veins across the venous resistance. This two-part pressure discharge is reflected in the PAOP decay curve. The initial rapid pressure drop approaches the pressure in the capillaries as the blood trapped in the downstream pulmonary capillaries equilibrates with pulmonary capillary pressure. This is followed by a slower pressure decrease approaching the PAOP as pulmonary capillary pressure equilibrates with pulmonary venous pressure. The initial pressure drop reflects the proximal arterial resistance, and the slower pressure drop reflects the distal, venous resistance. Normally two-thirds of the transpulmonary gradient pressure drop occurs over the arterial resistance, with approximately one-third of the pressure drop occurring over the venous resistance, as calculated from Gaar's equation: Pcap = PAOP + 0.4 (mPAP - PAOP). An increase in the pulmonary venous resistance increases the Pcap. Under these conditions the PAOP or LA pressure underestimates the Pcap[6-9].

In patients with PAH, Pcap measured with the occlusion technique is higher than normal and helps to locate the site of predominantly increased PVR in severe PH. The increased Pcap may be due to a previously assumed unimportant venous involvement in PAH. The results of Fesler *et al*[8], showed that compared to PAH, the arterial segment of the PVR (PVRa) is increased in chronic thromboembolic PH and decreased in pulmonary veno-occlusive disease, but isolated measurement of PVRa does not allow a differential diagnosis between these three types of severe PH.

The term PVR describes, in part, the forces opposing the flow across the pulmonary vascular bed. The equation traditionally used is based on the assumption that the pulmonary capillaries, as well as some others vessels in series, behave like a Poiseuille resistance, assuming a laminar type flow of a homogeneous Newtonian fluid. A single point measurement of mPAP, PAOP and cardiac output (CO), and derived PVR calculation may be misleading because the inherent assumptions of linearity and zero crossing of the (mPAP-PAOP)/CO relationship are not met. Therefore, a single point PVR determination at variable flow may underestimate or overestimate changes in the functional state of the pulmonary circulation. These errors or approximations can be limited by the definition of PVR as a multipoint pressure/flow line[2,3].

In clinical practice, determination of CO and cardiac index (CI) is typically done by either the thermodilution method or Fick method (using the Fick principle). Normal values are: CO: 4 to 8 L/min; CI: 2.6 to 4.2 L/m^2 per minute. Although a low CI ($\leqslant$ 2 L/m^2 per minute) has been shown to offer prognostic value for patients with PAH, the stroke volume index (SVI: CI/heart rate) should also be calculated in order to assessed the impact of heart rate on CO/CI values. An increased SVI with the same CI suggests better RV myocardial performance[7].

There is no technique that can be expected to provide flawless results for CO in the clinical setting. In the thermodilution method, cold or room-temperature solution is injected in the right atrium through the proximal port of the PAC. A curve generated by plotting the decline in PA temperature (℃) *vs* time (s). The area under the curve is inversely related to the CO because the injected solution is diluted by body temperature blood flow (e.g. higher area, lower CO). At least 3 measurements should be obtained and they should be within 10% of each other to improve accuracy. The physiological factors affecting accuracy of thermodilution CO determinations are: dysrhythmias, congenital heart defects (e.g. atrial septal defect), and severe tricuspid regurgitation (> 33% of right atrium area). The accuracy of the thermodilution technique in patients with low CO (overestimate) or severe tricuspid regurgitation (underestimate) has been questioned.

The Fick method measures pulmonary blood flow using principles described by Adolph Fick in 1870. This is obligatory when systemic-to-pulmonary shunt is present. It requires documentation of both O_2 consumption (VO_2) and the arteriovenous oxygen difference (Δ a-vO_2). Ideal determination of VO_2 can be done by collecting the patient's exhaled air over several minutes, or by metabolic carts at bedside using indirect calorimetry or assuming a basal O_2 consumption of 3.5 mL/kg or 125 mL/m^2. Calculation of Δa-vO_2 requires simultaneous determination of arterial and mixed venous O_2. When comparing changes in CO/CI by this method (e.g. before and after PH therapy), one must remember that significant changes in hemoglobin levels could account for differences in results.

Hoeper *et al*[12] showed, from 105 CO measurements in 35 patients, that thermodilution was equally accurate over a broad spectrum of CO values ranging from as low as 1.7 L/min to as high as 7.8 L/min. In addition, the agreement between the Fick method and thermodilution was not affected by the severity of tricuspid regurgitation.

Vasoreactivity testing is indicated in patients with idiopathic PAH, heritable PAH and associated anorexigen use to detect patients who can be treated with high doses of calcium channel blockers (class Ⅰ-level C)[1,5]. A positive response to vasoreactivity testing is defined as a reduction of mPAP ⩾ 10 mmHg to reach an absolute value of mPAP ⩽ 40 mmHg with an increased or unchanged CO (class Ⅰ-level C)[13]. Vasoreactivity testing should be performed only in referral centers and using nitric oxide (class Ⅱa-level C), iv epoprostenol, iv adenosine or inhaled iloprost (class Ⅱb-level C)[1].

In those patients with risk factors for LV diastolic dysfunction, acute vasoreactivity testing can lead to a significant increase in both LV end-diastolic pressure and PAOP, which unmasks the presence of impaired relaxation of the LV, resulting in acute pulmonary edema. A dramatic *v* wave pressure increase of the PAOP during vasoreactivity testing alerts the occurrence of this situation.

Some patients with pulmonary vascular disease are not symptomatic at rest, but have symptoms with exertion. This observation provides the potential for exercise or volume challenge during RHC to better diagnose early pulmonary vascular disease. These procedures have not been standardized and each cardiac catheterization laboratory has its own protocol. A typical amount of infused fluid varies between 500 to 1000 mL of normal saline, taking measurements every 250 mL. Challenge is interrupted when PAOP is > 18 mmHg or symptoms appear. An increase in PAOP to greater than 15 mmHg in response to exercise or fluid challenge suggests the presence of pulmonary venous hypertension, a condition with dramatically different management than PAH[1,4,7].

Calculation of PVR is essential in the management of patients with suspected PH. However, arterial pressure and ventricular load are also dependent on total arterial compliance (Cp). A simple approximation of Cp is the ratio of stroke volume to pulse pressure. In a prospectively obtained cohort of 104 patients with primary PH, Mahapatra *et al*[14] analyzed Cp as a predictor of mortality after adjusting for other modifiers of risk. During 4-year follow-up, 21 patients died and they demonstrated that Cp is a strong independent predictor of mortality in patients with PAH (ROC area of 0.91).

The hemodynamic prognostic parameters used in PAH are based on patient cohorts and have included: right atrium pressure > 12 mmHg, CI ⩽ 2 L/m^2 per minute, mixed venous O_2 saturation < 63% and in exercise RHC, the inability to augment CO and to reduce PVR. A Cp < 0.81 mL/mmHg predicted a < 40% probability of survival at 4 years, and a Cp > 2 mL/mmHg predicted a 100% survival. The presence of angina, presyncopal symptoms or frank syncope in response to exercise are also poor prognosis factors[1,14,15].

Partitioning of pulmonary vascular resistance in PH

The PA occlusion technique can be used in intact animals and patients for the determination of an effective Pcap, and for the partitioning of PVR into an arterial segment and a capillary-venous segment[6-9].

Recently, Kim *et al*[16], based on PVR being partitioned into large arterial (upstream, Rup) and small arterial plus venous (downstream) components, determined the risk of surgery in chronic thromboembolic pulmonary hypertension (CTEPH) patients with a highly elevated PVR who underwent pulmonary endarterectomy (PEA) through preoperative assessment of microvascular disease. Using a standard Swan-Ganz catheter, the pulmonary pressure signal was filtered using a two-pole digital low-pass filter with a cutoff at 18 Hz. A bi-exponential fitting of the pressure decay curve was then performed, which allowed estimation of the derived occlusion pressure (Poccl = Pcap). Rup (mPAP-Pcap/mPAP-PAOP) could identify CTEPH patients at high risk for residual PH (PVR > 3 wu) and poor outcome after PEA. In patients with small-vessel arteriopathy the Poccl pressure was higher (a longer time is required for the pressure to reach PAOP), and therefore the Rup was lower. In this cohort, the only postoperative deaths occurred in patients with Rup preoperatively estimated at less than 60%, indicating significant down-stream, inoperable, small-vessel involvement. Thus, patients with lower Rup appear to be at high risk for persistent PH and death after PEA. They concluded that a Rup < 60% appears to be at highest risk secondary to a large microvascular disease[16].

NOVEL INVASIVE HEMODYNAMIC PARAMETERS

Assessment of the pulmonary arterial pressure waveform

Chronic pulmonary hypertension results from an increase in PVR, which is a simple measure of the opposition to the mean component of flow. However, given the low resistance/high compliance nature of the pulmonary circulation, the pulsatile component of hydraulic load is also critical to consider. The fact that the mean and the pulsatile components of flow are dependent on different portions of the pulmonary circulation suggests that they can be controlled separately, without much overlap. Pulmonary arterial pulse pressure (pPAP) indicates the amplitude of pulsatile stress. pPAP is mainly determined by both the characteristics of ventricular ejection and arterial compliance, so that the lower the compliance, the higher the pPAP. It has been reported that pulsatility as the ratio of pPAP to mPAP [i.e. fractional pulse pressure (fPp)] in CTEPH was larger than in PAH and that in patients with severe haemodynamic impairment (PVR > 1000-1100 dyne s/cm^5), fPp in addition to PVR might be useful in predicting the outcome of PEA. fPp might be low in CTEPH with inaccessible distal thrombi and/or secondary pulmonary hypertensive change[17].

The main pulmonary arterial pressure waveform (PAPW) qualitative morphology analysis may be of diagnostic and prognostic value in patients with PH. A main PAPW is the result of an interaction between the heart and the arterial system[18]. We can estimate the amplitude of the forward (Pi-dPAP) and reflected (sPAP-Pi) pressure waves depending on the inflection point (Pi), where

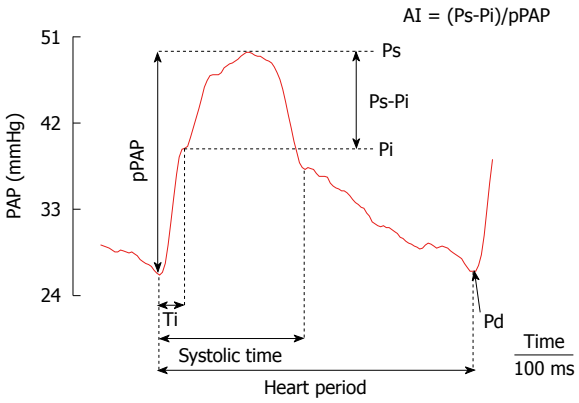

Figure 4 Typical pulmonary artery pressure tracing showing the PA waveform analysis.

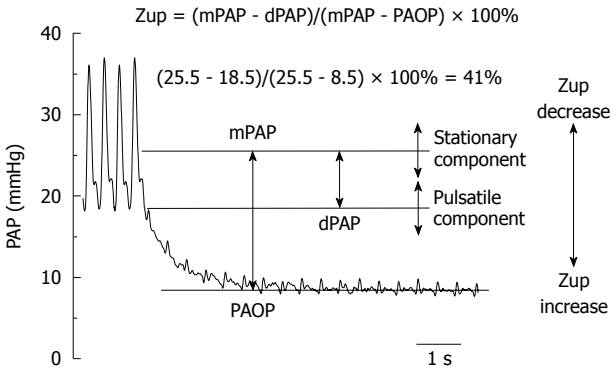

Figure 5 Example of the pulmonary artery decay curve showing the calculus of Zup.

dPAP and sPAP are diastolic and systolic PAP. Since, in most cases, the inflection in pressure was smooth, the Pi is defined as the time at which the first derivative of PAP (dPAP/dt) reached its first minimum. The augmentation index (AI) can be estimated by the ratio of sPAP-Pi to pPAP and the timing of wave reflection was quantified by the inflection time (Ti, Figure 4). Therefore, PAPW with amplitude sPAP-dPAP is composed of a forward traveling wave, with amplitude Pi-dPAP generated by the RV ejection and a later arriving reflected wave, with amplitude sPAP-Pi from the periphery. The forward wave is dependent largely upon elastic properties of the main PA and is not influenced by wave reflections. The reflected wave is dependent upon the elastic properties of the entire arterial tree, pulse wave velocity, the round-trip travel time of the wave from the heart to the periphery and back, and the distance to the major reflecting sites[18,19].

Castelain *et al*[20] analyzed high-fidelity PA pressure in 14 patients with CTEPH (n = 7) and primary PH (n = 7). They showed that CTEPH patients had shorter Ti and higher AI, with an increased and anticipated wave reflection as compared with primary PH, suggesting differences in the pulsatile component of the RV afterload.

Finally, the extra workload due to wave reflection (wasted pressure or energy the RV must generate during ejection) can also be estimated as EW = [(Ts-Ti)(sPAP-Pi)π/2], where Ts corresponds to systolic time. We have shown that under steady isobaric condition, RV pulsatile load (AI) is attenuated during active PH by maintaining main PA stiffness (Pi-dPAP) and reducing the extent of the reflected wave (sPAP-Pi, EW)[21].

In clinical settings, PAPW analysis might help in evaluating the severity of different forms of PH. Vasculopathy of PAH involves both distal resistive arteries and proximal conduit arteries, which would determine different dynamic RV afterload with different RV adaptation.

Partitioning of pulmonary vascular impedance in PH

As was mentioned previously, the PAPW mainly depends on both the characteristics of ventricular ejection and the properties of the arterial circulation, which determine the compliance (cushioning capacity) and the transmission properties of the arterial system (timing and intensity of arterial wave). The extent of vascular obstruction and associated vasculopathy are the major determinants of the mPAP. However, a more proximal occlusive site and a higher PA stiffness determine an earlier and greater wave reflection, which in turn increases sPAP and decreases dPAP pressures ("ventricularization" of the PA pressure curve), with non significant changes in mPAP and PAOP[22,23]. Pulmonary vascular capacitance (Cp) reflects the ability of the pulmonary vessels to dilate during systole and recoil during diastole. By storing blood during systole, a high capacitance tree dampens the sPAP, and by recoiling during diastole, a high Cp increases dPAP.

Taking into account that the difference between mPAP and PAOP is in proportion with PVR, and that dPAP depends on PA recoil during diastole and the timing and degree of wave reflection, as well as heart rate, mPAP - PAOP is a measure of the steady component of afterload, while mPAP - dPAP is an indirect measure of the pulsatile component of the afterload. The ratio between both (mPAP-dPAP/mPAP-PAOP, named upstream pulmonary vascular impedance, Zup) would be evaluated pulsatile and steady afterload components simultaneously (Figure 5). Therefore, Zup is in proportion to the upstream impedance (a higher upstream impedance determines lower dPAP and vice versa)[24].

We recently analyzed preoperative Zup in operable (Ⅰ, n = 32) and inoperable (Ⅱ, n = 31) CTEPH patients to compare it with PVR, Cp and fPp. In I, 5 patients died during the first 30 d after surgery and had higher basal PVR and lower basal Zup, Cp index and fPp than survivors ($P < 0.05$). Patients with residual pulmonary hypertension (RPH) had significantly lower Zup and lower improvement of Cp index and pulse pressure 1 year after PEA, than patients without residual PH. Although, operable (Ⅰ) and non-operable (Ⅱ) patients showed the same mPAP, basal Zup in I was significantly higher than in Ⅱ (58 ± 15; 50 ± 14%). Zup showed the highest ROC area for discriminating poor outcome (0.923) with a cut-off value of 47%. We concluded that early mortality and RPH after PEA may be better discriminated by preoperative Zup than by steady (PVR) or pulsatile (fPp) pulmonary afterload alone. Among operable patients with good

evolution 1 year after PEA, a lower Zup could be predictive of RPH, which is associated with a lower improvement of capacitance index and pulse pressure[25].

The lower Zup in inoperable CTEPH (Ⅱ) and in idiopathic PAH patients (isobaric steady component analysis) with respect to operable CTEPH (Ⅰ), is in accordance with a more diffuse distribution of RV afterload and would be related to different vascular wall remodeling (thrombus organization and small vessel arteriopathy)[25,26]. This could also explain why CTEPH lung is virtually indistinguishable from IPAH lung at the histopathologic level at autopsy and in biopsy studies.

Evaluation of elastic pulmonary arteries by intravascular ultrasound

PAH is a disease of the arterial vessel wall that affects both steady and pulsatile components of the pulmonary arterial hemodynamics. PA stiffness is an important factor governing dynamic afterload. It has also been reported that proximal PA stiffness may increase early in the course of PH, suggesting a potential contributory role of PA stiffness in the development and progression of PH[27]. Increased stiffness observed in PA hypertension may be secondary to elevated distending pressures and/or to structural changes of the PA wall.

Intravascular ultrasound (IVUS) assessment of the pulmonary circulation has been proposed as a technique to evaluate the arterial wall changes observed in the elastic pulmonary vessels of patients diagnosed with PAH. There has been preliminary data on *in vivo* PA pulsatility evaluation in PA hypertension[28]. The arterial pulsatility depends on the the intraluminal pressure and on the intrinsic viscoelastic properties of the arterial wall. The absence of the relation between pulsatility and hemodynamic variables, described in some studies, suggests that the changes in pulmonary vessel remodeling may be responsible for the functional alterations shown by IVUS. It has already been reported that only indexes relating pressure and diameter followed qualitative changes of the elastic incremental modulus (a true evaluator of the elastic status of the vessel wall from the stress-strain relationship) in an animal model of acute PH[29]. Rodés-Cabau *et al*[30] demonstrated PA wall abnormalities in all patients with primary PH, mostly eccentric. Although the severity of the impaired PA functional state did not correlate with hemodynamic variables, it was associated with mortality at follow up of these patients.

We recently evaluated local PA stiffness in a cohort of patients with PAH and its relation with dynamic afterload. This study showed that only local PA stiffness indexes normalized by pulse pressure correlated with global capacitance and resistance properties of the pulmonary arterial tree. Neither the hemodynamic capacitance index nor pulmonary vascular resistance correlated with IVUS pulsatility[31].

Elastic modulus, local and dynamic compliance and distensibility may be an expression of the intrinsic PA wall remodeling and viscoelastic properties, and should be used to better understand the histopathological changes and response to treatment of the pulmonary circulation in PAH.

Analysis of RV function and coupling to the pulmonary circulation

Instead of trying to quantify the RV afterload by different approaches, it might be more appropriate to quantify the RV function directly and to couple to the pulmonary circulation. Sagawa *et al*[32] showed that this can be done graphically using a ven-tricular pressure-volume diagram. The diagram allows for the determination of maximal or end-systolic ventricular elastance (Ees, end-systolic pressure on end-systolic volume), which is the best possible load-independent measurement of contractility, of arterial elastance (Ea, end-systolic pressure on stroke volume), as a measurement of afterload as it is 'seen' by the ventricle, and of the calculation of an Ees/Ea ratio as a measurement of the coupling of ventricular to arterial function.

The complex geometry of the RV makes functional evaluations with measurement of instantaneous volume changes technically difficult, and the determination of Ees may be unreliable because of the triangular shape of the RV pressure-volume loop resulting from the fact that RV ejection continues after end-systole. This difficulty in measuring instantaneous RV volume is overcome using a single-beat method, which derives a systolic pressure-volume relationship from instantaneous RV pressure and an integration of pulmonary arterial flow[3]. On such a pressure-volume curve, it is easy to determine graphically Ees and Ea. The optimal value of the Ees/Ea ratio, compatible with flow output at a minimal energy cost, is between 1 and 2. Patients with severe PH present with a decreased elastance ratio, in spite of an adaptative increase in systolic function, which underscores that RV failure in the face of increased afterload is a relative notion. Recently, Kuehne *et al*[33] used magnetic resonance imaging together with RV pressure measurements to generate pressure-volume loops and to determine Ees and Ea values in patients with PAH. As compared with controls, RV Ees was increased from 5.2 ± 0.9 mmHg/mL per 100 g to 9.2 ± 1.2 mmHg/mL per 100 g ($P < 0.05$), but RV Ees/Ea was decreased from 1.9 ± 0.4 to 1.1 ± 0.3 ($P < 0.05$), indicating an increased RV contractility in response to increased afterload that was, however, insufficiently coupled to its hydraulic load, with inefficient mechanical work production.

Further studies are needed to confirm that right ventriculo-arterial decoupling accounts for a decreased aerobic exercise capacity by a limitation of cardiac output adaptation to peripheral demand.

CONCLUSION

While traditional resting RHC techniques still remain the gold standard for diagnosing PH and managing patients on therapy, there are novel invasive techniques that do not add significant time or risk to the procedure that add greatly to our understanding of the RV, pulmonary circulation, and the interaction between them, and for the interpretation of data from clinical trials as well.

REFERENCES

1 **Badesch DB**, Champion HC, Sanchez MA, Hoeper MM, Loyd JE, Manes A, McGoon M, Naeije R, Olschewski H, Oudiz RJ, Torbicki A. Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; **54**: S55-S66

2 **Champion HC**, Michelakis ED, Hassoun PM. Comprehensive invasive and noninvasive approach to the right ventricle-pulmonary circulation unit: state of the art and clinical and research implications. *Circulation* 2009; **120**: 992-1007

3 **Naeije R**, Huez S. Right ventricular function in pulmonary hypertension: physiological concepts. *Eur Heart J* 2007; **9** Suppl: H5-H9

4 **Chemla D**, Castelain V, Hervé P, Lecarpentier Y, Brimioulle S. Haemodynamic evaluation of pulmonary hypertension. *Eur Respir J* 2002; **20**: 1314-1331

5 **Escribano Subias P**, Barberà Mir JA, Suberviola V. Current diagnostic and prognostic assessment of pulmonary Hypertension. *Rev Esp Cardiol* 2010; **63**: 583-596

6 **Takala J**. Pulmonary capillary pressure. *Intensive Care Med* 2003; **29**: 890-893

7 **Soto FJ**, Kleczka JF. Cardiopulmonary hemodynamics in pulmonary hypertension: pressure tracings, waveforms, and more. *Adv Pulm Hypertension* 2008; **7**: 386-393

8 **Fesler P**, Pagnamenta A, Vachiéry JL, Brimioulle S, Abdel Kafi S, Boonstra A, Delcroix M, Channick RN, Rubin LJ, Naeije R. Single arterial occlusion to locate resistance in patients with pulmonary hypertension. *Eur Respir J* 2003; **21**: 31-36

9 **Ganter CC**, Jakob SM, Takala J. Pulmonary capillary pressure. A review. *Minerva Anestesiol* 2006; **72**: 21-36

10 **Halpern SD**, Taichman DB. Misclassification of pulmonary hypertension due to reliance on pulmonary capillary wedge pressure rather than left ventricular end-diastolic pressure. *Chest* 2009; **136**: 37-43

11 **Cope DK**, Grimbert F, Downey JM, Taylor AE. Pulmonary capillary pressure: a review. *Crit Care Med* 1992; **20**: 1043-1056

12 **Hoeper MM**, Maier R, Tongers J, Niedermeyer J, Hohlfeld JM, Hamm M, Fabel H. Determination of cardiac output by the Fick method, thermodilution, and acetylene rebreathing in pulmonary hypertension. *Am J Respir Crit Care Med* 1999; **160**: 535-541

13 **Sitbon O**, Humbert M, Jaïs X, Ioos V, Hamid AM, Provencher S, Garcia G, Parent F, Hervé P, Simonneau G. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation* 2005; **111**: 3105-3111

14 **Mahapatra S**, Nishimura RA, Sorajja P, Cha S, McGoon MD. Relationship of pulmonary arterial capacitance and mortality in idiopathic pulmonary arterial hypertension. *J Am Coll Cardiol* 2006; **47**: 799-803

15 **Barberà JA**, Escribano P, Morales P, Gómez MA, Oribe M, Martínez A, Román A, Segovia J, Santos F, Subirana MT. [Standards of care in pulmonary hypertension. Consensus statement of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) and the Spanish Society of Cardiology (SEC)]. *Rev Esp Cardiol* 2008; **61**: 170-184

16 **Kim NH**, Fesler P, Channick RN, Knowlton KU, Ben-Yehuda O, Lee SH, Naeije R, Rubin LJ. Preoperative partitioning of pulmonary vascular resistance correlates with early outcome after thromboendarterectomy for chronic thromboembolic pulmonary hypertension. *Circulation* 2004; **109**: 18-22

17 **Tanabe N**, Okada O, Abe Y, Masuda M, Nakajima N, Kuriyama T. The influence of fractional pulse pressure on the outcome of pulmonary thromboendarterectomy. *Eur Respir J* 2001; **17**: 653-659

18 **Nichols WW**, Singh BM. Augmentation index as a measure of peripheral vascular disease state. *Curr Opin Cardiol* 2002; **17**: 543-551

19 **Nakayama Y**, Nakanishi N, Sugimachi M, Takaki H, Kyotani S, Satoh T, Okano Y, Kunieda T, Sunagawa K. Characteristics of pulmonary artery pressure waveform for differential diagnosis of chronic pulmonary thromboembolism and primary pulmonary hypertension. *J Am Coll Cardiol* 1997; **29**: 1311-1316

20 **Castelain V**, Hervé P, Lecarpentier Y, Duroux P, Simonneau G, Chemla D. Pulmonary artery pulse pressure and wave reflection in chronic pulmonary thromboembolism and primary pulmonary hypertension. *J Am Coll Cardiol* 2001; **37**: 1085-1092

21 **Grignola J**, Devera L, Ginés F. Main pulmonary artery pressure waveform analysis: a time-domain approach for complete hemodynamic evaluation during pulmonary hypertension. *Circulation* 2008; **118**: e379

22 **Grant BJ**, Lieber BB. Clinical significance of pulmonary arterial input impedance. *Eur Respir J* 1996; **9**: 2196-2199

23 **Chemla D**, Castelain V, Simonneau G, Lecarpentier Y, Hervé P. Pulse wave reflection in pulmonary hypertension. *J Am Coll Cardiol* 2002; **39**: 743-744

24 **Grignola JC**, Ruiz-Cano MJ, Escribano P, Cortina J, Velazquez T, Gomez-Sanchez MA, Delgado J, Saenz De La Calzada C. Assessment of early outcome and residual pulmonary hypertension after pulmonary endarterectomy by preoperative analysis of dynamic right ventricular afterload. *Eur Heart J* 2009; **30** Suppl: 110

25 **Ruiz-Cano MJ**, Grignola JC, Escribano P, Cortina J, Velázquez T, Gómez Sánchez MA, Delgado JF, Sáenz de la Calzada C. Preoperative partitioning of pulmonary vascular impedance: a novel hemodynamic index for operable and inoperable chronic thromboembolic pulmonary hypertension. *J Am Coll Cardiol* 2010; **55** (Suppl 1): A171

26 **Grignola JC**, Ruiz-Cano MJ, Escribano P, Gomez-Sanchez MA, Tello De Meneses R, Delgado J, Jimenez Lopez-Guarch C, Saenz De La Calzada C. Isobaric analysis of pulmonary arterial compliance of idiopatic and chronic thromboembolic pulmonary hypertension: correlation with right ventricular remodeling. *Eur Heart J* 2009; **30** Suppl: 108

27 **Sanz J**, Kariisa M, Dellegrottaglie S, Prat-González S, Garcia MJ, Fuster V, Rajagopalan S. Evaluation of pulmonary artery stiffness in pulmonary hypertension with cardiac magnetic resonance. *JACC Cardiovasc Imaging* 2009; **2**: 286-295

28 **Bressollette E**, Dupuis J, Bonan R, Doucet S, Cernacek P, Tardif JC. Intravascular ultrasound assessment of pulmonary vascular disease in patients with pulmonary hypertension. *Chest* 2001; **120**: 809-815

29 **Santana DB**, Barra JG, Grignola JC, Ginés FF, Armentano RL. Pulmonary artery smooth muscle activation attenuates arterial dysfunction during acute pulmonary hypertension. *J Appl Physiol* 2005; **98**: 605-613

30 **Rodés-Cabau J**, Domingo E, Román A, Majó J, Lara B, Padilla F, Anívarro I, Angel J, Tardif JC, Soler-Soler J. Intravascular ultrasound of the elastic pulmonary arteries: a new approach for the evaluation of primary pulmonary hypertension. *Heart* 2003; **89**: 311-315

31 **Grignola JC**, Domingo E, Bravo C, Aguilar R, Lopez-Messeguer M, Vazquez M, Roman A. Local pulmonary artery stiffness indexes are correlated with steady and pulsatile components of right ventricular afterload in pulmonary arterial hypertension. *J Am Coll Cardiol* 2010; 55 (Suppl 1): A172

32 **Sagawa K**, Maughan L, Suga H, Sunagawa K. Cardiac contraction and the pressure-volume relationship. New York: Oxford University Press, 1988

33 **Kuehne T**, Yilmaz S, Steendijk P, Moore P, Groenink M, Saaed M, Weber O, Higgins CB, Ewert P, Fleck E, Nagel E, Schulze-Neick I, Lange P. Magnetic resonance imaging analysis of right ventricular pressure-volume loops: in vivo validation and clinical application in patients with pulmonary hypertension. *Circulation* 2004; **110**: 2010-2016

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TOPIC HIGHLIGHT

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Effects of interventions on oxidative stress and inflammation of cardiovascular diseases

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Abstract

Excessive oxidative stress and low-grade chronic inflammation are major pathophysiological factors contributing to the development of cardiovascular diseases (CVD) such as hypertension, diabetes and atherosclerosis. Accumulating evidence suggests that a compromised anti-oxidant system can lead to excessive oxidative stress in cardiovascular related organs, resulting in cell damage and death. In addition, increased circulating levels of pro-inflammatory cytokines, such as tumor necrosis factor α, interleukin-6 and C-reactive protein, are closely related to morbidity and mortality of cardiovascular complications. Emerging evidence suggests that interventions including nutrition, pharmacology and exercise may activate expression of cellular anti-oxidant systems *via* the nuclear factor erythroid 2-related factor 2-Kelch-like ECH-associated protein 1 signaling pathway and play a role in preventing inflammatory processes in CVD. The focus of the present review is to summarize recent evidence showing the role of these anti-oxidant and anti-inflammatory interventions in cardiovascular disease. We believe that these findings may prompt new effective pathogenesis-oriented interventions, based on the exercise-induced protection from disease in the cardiovascular system, aimed at targeting oxidant stress and inflammation.

Key words: Anti-oxidant; Exercise; Nuclear factor erythroid 2-related factor 2-Kelch-like ECH-associated protein 1 signaling; Pro-inflammatory cytokines

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INTRODUCTION

Cell damage that occurs by insults such as oxidative stress and toxicants may contribute to atherosclerosis, coronary artery disease, stroke, myocardial infarction, Alzheimer's disease, Parkinson's disease and cancer[1-5]. Of these diseases, excessive oxidative stress and chronic inflammation are both major characteristics of the pathology seen in type 2 diabetes (T2D), cardiovascular diseases (CVD) and the aging process[1,6]. Specifically, T2D and CVD are associated with increased production of reactive oxygen

species (ROS) and compromised endogenous anti-oxidant defense. Oxidative stress is tightly regulated by a balance between production and removal of ROS. ROS are natural by-products of metabolism and these molecules play important roles in cell signaling. However, excessive levels of ROS can be toxic to cells, i.e. whenever the expression of anti-oxidant enzymes, including superoxide dismutases (SODs), heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase-1 (NQO-1), catalase and thioredoxin are not sufficient to control ROS and minimize ROS-induced damage[3]. A compromised anti-oxidant defense system can lead to excessive oxidative stress and ultimately result in cell damage[7-9].

Recent work has indicated that chronic inflammation is an important pathophysiological factor in the development of T2D and CVD, with increased circulating levels of pro-inflammatory cytokines, such as circulating C-reactive protein (CRP), tumor necrosis factor (TNF)-α, interleukin (IL)-6 and IL-1β[10-14]. Opposing the pro-inflammatory cytokines, anti-inflammatory cytokines, such as IL-10 and adiponectin, are inversely correlated with the incidence of these diseases. These anti-inflammatory cytokines play a role in inhibiting the action of TNF-α on endothelial cell adhesion, reducing nuclear factor (NF)-κB activation, and delaying macrophage foam-cell development[15-18]. T2D and CVD are associated with aging and a sedentary lifestyle; however, emerging evidence suggests that the anti-inflammatory effects of exercise and/or physical activity can reduce mortality and morbidity of these patients[19-22]. However, the mechanism(s) that confer anti-inflammatory effects following an exercise training regimen have not been clearly identified.

This review addresses the effects of interventions, such as nutrition, pharmacology, genetics and exercise on anti-oxidant systems and on inflammation.

ROLE OF INTERVENTIONS IN ENDOGENOUS ANTIOXIDANT SIGNALING

The anti-oxidant defense system is regulated, in large part, by a transcription factor termed nuclear factor erythroid 2-related factor 2 (Nrf2), which is a member of the cap 'n' collar subfamily of the basic leucine zipper transcription factors[5]. Under normal physiological conditions, Nrf2 is bound to a cytoplasmic repressor, termed Kelch-like ECH-associated protein 1 (Keap1)[23]. Keap1 functions as a substrate adaptor for a Cullin3-dependent ubiquitin ligase and targets Nrf2 for degradation by the proteasome[24-26]. The substrate adaptor function of Keap1 is inactivated in response to a range of oxidative and electrophilic stimuli such as ROS, diethyl malonate and certain disease processes, resulting in the accumulation of Nrf2, which enters the nucleus and activates expression of anti-oxidant genes[5,9]. Although most investigators believe that Keap1-mediated repression occurs in the cytoplasm, several studies have shown that Nrf2 and Keap1 can shuttle between the nucleus and the cytoplasm[27-29]. In the nucleus, Nrf2 forms a heterodimer with members of the small musculo-aponeurotic fibrosarcoma (Maf) transcription factor family. These Nrf2/Maf heterodimers bind to anti-oxidant response elements present in the promoters of numerous anti-oxidant genes, including NQO-1, glutathione S-transferase, glutathione peroxidase (GPx), catalase and HO-1[5,9,30-32] (Figure 1). Nrf2 is widely expressed and it has been studied in many different tissues[7,33,34]. In the cardiovascular system, it has been shown that ischemia/reperfusion (I/R) down-regulates Nrf2 protein expression in rat heart and that aging decreases glutathione synthesis *via* diminished Nrf2 signaling in rat vascular endothelial and smooth muscle cells, suggesting that Nrf2 may play a critical role in the development of CVD in the aged population[6,35]. He *et al*[30] have shown a functionally decreased contractility when Nrf2 is genetically deleted from cardiomyocytes due to a marked increase in high-glucose oxidative stress and apoptosis.

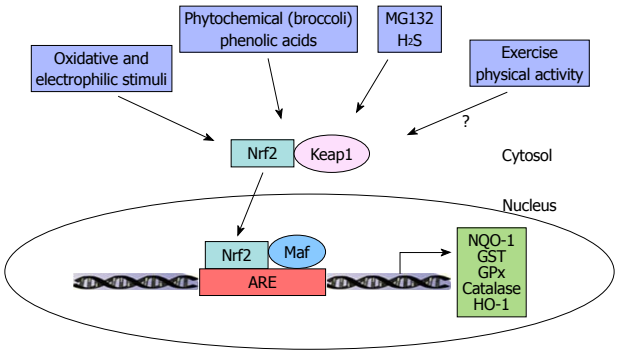

Figure 1 The role of interventions in nuclear factor erythroid 2-related factor 2-Kelch-like ECH-associated protein 1 signaling pathway. Nuclear factor erythroid 2-related factor 2 (Nrf2) can be activated by interventions such as nutrition (phytochemical, phenolic acids), pharmacology (MG132, H_2S) and oxidative and electrophilic stimuli. Under basal conditions, Nrf2 is sequestered in the cytosol by binding with Kelch-like ECH-associated protein 1 (Keap1). On activation, Nrf2 can be released from Keap1 and translocated into the nucleus. Nrf2 forms a heterodimer with musculo-aponeurotic fibrosarcoma (Maf) and antioxidant response element (ARE) and regulates phase II anti-oxidant enzymes. NQO-1: NAD(P)H quinone oxidoreductase-1; GST: Glutathione S-transferase; GPx: Glutathione peroxidase; HO-1: Heme oxygenase-1.

Role of nutrition in antioxidant signaling

Numerous studies have indicated that increased oxidative stress may be involved in the pathogenesis of CVD. Several animal models suggest that when endogenous anti-oxidant systems are overwhelmed, exogenous anti-oxidant supplementation can be used for preventive and/or therapeutic intervention of oxidative cardiovascular disorders[35,36]. Phenolic acids are a group of compounds that are widely distributed in natural plant foods including fruits, vegetables and whole grains[36]. Yeh *et al*[36] have shown that 14 d of oral gavage (100 mg/kg) of phenolic acids in male rats increased anti-oxidant capacity *via* SOD-1, GPx and catalase, while HO-1 mRNA increased *via* Nrf2 signaling in the heart. Other phytochemicals, such as those found in broccoli sprouts may confer protection against

cancer, although little is known about these effects on the cardiovascular system[37,38]. Recently, Mukherjee *et al*[35] have tested if daily consumption of broccoli, which contains sulforaphane and selenium for 1 mo could be beneficial to the heart. They have found that broccoli induced cardioprotection in I/R through the induction of HO-1[35].

Role of pharmacology and genetics in antioxidant signaling

The proteasome system uses a ubiquitin tag to activate the major intracellular protein degradation in eukaryotic cells[39]. The ubiquitin-proteasome system is critical for degradation of proteins related to the cell cycle and apoptosis[40,41]. In this sense, proteasome inhibition has been highlighted as a promising therapeutic target for treatment of human diseases. For instance, proteasome inhibitors have been proposed as an anti-inflammatory treatment *via* inhibition of NF-κB[42]. As steady-state levels of Nrf2 increase following proteasome inhibition, Dreger *et al*[39] have suggested that non-toxic inhibition of the ubiquitin-proteasome system by MG132 (0.5 μmol/L for 48 h) may contribute to protection of rat cardiomyocytes against oxidative stress *via* Nrf2-mediated transcriptional activation of anti-oxidants. Calvert *et al*[43] showed that hydrogen sulfide (H_2S) may be an attractive pharmacological agent for the treatment of CVD by up-regulating anti-oxidants and anti-apoptogens. They showed that 100 μg/kg precondition by H_2S in the form of sodium sulfide resulted in protection against myocardial I/R injury in a mouse model by increasing endogenous anti-oxidant defenses *via* an Nrf2-dependent manner. In this study, Nrf2 deficient mice showed an exacerbated injury in response to I/R, suggesting that Nrf2 may play an important cardio-protective role in heart disease[43]. On the other hand, Sussan *et al*[44] have shown that disruption of Nrf2 in apolipoprotein E (ApoE) knockout mice significantly decreased atherosclerotic plaque after 20 wk of high-fat diet. However, Nrf2 knockout mice showed increased susceptibility to pulmonary emphysema, asthma and sepsis due to increased oxidative stress and inflammation[44]. This study suggested that Nrf2 might promote atherosclerotic plaque development through a mechanism separate from oxidative stress. More studies are required to fully understand the contribution of Nrf2 signaling in regards to atherosclerosis.

Role of exercise and physical activity in antioxidant processes

A sedentary lifestyle is a risk factor for T2D and CVD with several clinical studies illustrating a reduction of mortality and morbidity in physically active individuals compared to sedentary individuals[45-47]. Exercise or physical activity may contribute to improvement of insulin resistance *via* improved insulin action, improved vascular function *via* increase of nitric oxide (NO) bioavailability, and by increasing ROS-detoxification and decreasing ROS generation[48-53]. Since generation of ROS is a normal result of aerobic metabolism, it is efficiently removed by cellular anti-oxidant systems under physiological conditions. Several studies have shown that chronic exercise training increases SOD gene expression in vascular systems. Exercise training increased SOD-3 gene expression in mice aorta in NO-dependent manner and up-regulated SOD-1 in Yucatan miniature pig aortas[50,51]. Recently, Moien-Afshari *et al*[54] have suggested that low intensity exercise training increased SOD-1 protein expression, whereas moderate intensity increased SOD-2 gene expression in diabetic mice aorta with improved NO availability. Even though many studies have shown that exercise and physical activity up-regulated anti-oxidants such as SODs in cardiovascular systems, little is known about how exercise and physical activity may increase phase Ⅱ anti-oxidant systems *via* the Nrf2-Keap1 signaling pathway[50,51,54,55]. Even though there are no clear studies to determine if exercise training may alter Nrf2 signaling, Niess *et al*[56] have shown that leukocytes from endurance trained athletes down-regulate the baseline expression of HO-1, presumably due to the adaptation mechanism of exercise training. Since HO-1 is an anti-oxidant protein that is mainly induced through the Nrf2-Keap1 signaling pathway, exercise training may down-regulate Nrf-2 signaling in humans. However, more studies are needed to further elucidate the effect of exercise on Nrf2 mechanisms in the cardiovascular system.

ROLE OF EXERCISE IN INFLAMMATION

Effect of acute exercise on inflammation

The effect of acute exercise on pro-inflammatory cytokines release has been a matter of considerable debate, since although a majority of studies have reported that acute exercise simulates release of inflammatory cytokine[57-61], some studies have also shown that acute exercise did not change levels of the pro-inflammatory cytokines TNF-α and IL-1β[58,61-63]. These discrepant findings suggest that the level of pro-inflammatory cytokines during and following exercise is dependent on several factors including the pathological condition, intensity and duration of exercise, and timing of sampling[64]. For example, plasma concentration and muscle mRNA expression of TNF-α are elevated in chronic obstructive pulmonary disease patients during continuous moderate-intensity exercise (for 11 min at 40% VO_{2max}) whereas no change occurs in normal individuals[64]. Although the circulating level of TNF-α is not altered during low intensity and long duration of two-leg knee extensor exercise, short duration and high intensity of cycling exercise, approximately 80% VO_{2max}, increases the circulating level of pro-inflammatory cytokines, IL-4, IL-6, TNF-α, interferon (IFN)-γ and anti-inflammatory cytokine such as IL-1β and IL-10[59,64]. Ostrowski *et al*[57] found that IL-6 and IL-1 receptor antagonist (IL-1ra) levels were enhanced during 2 h of continuous exercise (measured at every 30 min for 2 h) and following exercise, despite no change in the TNF-α level. Of these multiple pro-inflammatory cytokines, IL-6 is the most responsive cytokine that is increased during and following exercise and it is related to exercise intensity, duration, and muscle mass recruited[65,66]. Contracting skel-

etal muscle is one of the major sources of IL-6 produced during exercise. For example, during even moderate intensity of exercise (50% of maximal power output), 3 h of dynamic two-legged knee-extensor, muscle IL-6 mRNA expression and plasma concentration of IL-6 is increased 16-fold and 20-fold, respectively[67]. An even greater amount of IL-6 is produced in higher intensity and longer duration of exercise[66]. More interestingly, Petersen *et al*[66] suggest that IL-6 produced from working muscle can play a hormone-like role that stimulates lipolysis and fat oxidation in adipose tissue and induces gluconeogenesis in liver that may enhance exercise capacity. Moreover, IL-6 has been suggested as an anti-inflammatory cytokine because some studies have shown that an infusion of IL-6 decreases TNF-α production in healthy humans and stimulates the release of anti-inflammatory cytokines, IL-1ra and IL-10[68,69]. However, IL-6 is a well-established pro-inflammatory cytokine that is closely linked to various CVD and morbidity and mortality of several diseases. One possible explanation of a paradoxical role of IL-6 as an inflammatory cytokines and as a mediator of beneficial adaptation to exercise is the location of IL-6 production. Muscle contracting-induced local production of IL-6 may play a positive role in lipid and carbohydrate metabolism during exercise whereas systemic IL-6 may result in a negative consequence of tissue injury, chronic infection and diseases.

Effect of chronic exercise on inflammation

Exercise training and/or a high level of physical activity has a beneficial effect on inflammation through a reduction of pro-inflammatory cytokines and an increase in anti-inflammatory cytokines. Cross-sectional studies show lower plasma levels of IL-6, TNF-α and CRP while higher plasma levels of IL-10 and adiponectin occur in physically active individuals compared to physically inactive groups[16,70-72]. Exercise decreases pro-inflammatory cytokines and indicators of systemic inflammation. For example, long-term exercise (for 6 mo) significantly attenuates the production of pro-inflammatory cytokines, TNF-α and IFN-γ, and enhances the anti-inflammatory cytokine IL-10 in individuals at risk of developing ischemic heart disease[73]. Participation in an exercise training program for 6 mo in patients with stable chronic heart failure (CHF) significantly decreases the mRNA expression of TNF-α, IL-6, IL-1β in skeletal muscle, compared to the healthy individuals[74]. On the other hand, some studies demonstrate that the levels of pro-inflammatory cytokines are not significantly altered after exercise training in the obese individuals and healthy elderly[75-77]. This discrepancy may be derived from differences in experimental design and disease status of the subjects. The studies showing the effectiveness of exercise training on pro-inflammatory cytokines investigated the patients with severe disease conditions such as CHF and ischemic heart disease where basal levels of cytokines were already elevated compared to the healthy individuals before the exercise training[73,74]. In contrast, no apparent change in pro-inflammatory cytokines is shown in relatively less severe conditions, such moderate obesity (approximately 40% of % body fat) and aging (approximately 66 years old)[75-77]. Moreover, local change in inflammation after exercise training is an important factor to be considered. For example, mRNA expression of pro-inflammatory cytokines, TNF-α, IL-6, IL-1β in skeletal muscle are reduced after exercise training although the circulating levels of those cytokines are not changed[74]. This finding suggests that exercise training does not play a role in reducing systemic inflammation and is not effective enough to reduce the circulating levels of cytokines. However, regional expression of cytokines in skeletal muscle are affected. This regional reduction of pro-inflammatory cytokines in skeletal muscle may have a beneficial effect in skeletal muscles homeostasis despite the lack of effect on systemic inflammation.

Mechanisms of anti-inflammatory effect of exercise

As previously described, acute exercise stimulates production of pro-inflammatory cytokines and superoxide ($O_2^{\bullet}$) that can cause the tissue injury. Interestingly, exercise induced pro-inflammatory cytokines are triggers to generate the anti-inflammatory cytokines such as IL-10, IL-1ra and transforming growth factor β and the anti-oxidant, SOD-2 that have protective functions[58,60,63]. The major role of these cytokines is to recruit neutrophils and monocytes into injured tissue for repair[78]. During this process, anti-inflammatory cytokines and anti-oxidant mechanisms can be initiated and limit the inflammatory reaction in response to exercise. It is suggested that this stimulated anti-inflammatory mechanism, in turn, may down-regulate production of pro-inflammatory cytokines during and following exercise.

CONCLUSION

Oxidative stress plays a critical role in the pathology of CVD. Exogenous anti-oxidant supplementations such as broccoli, curcumin and phenolic acids as well as stimulators of endogenous pathways such as MG132, H_2S and exercise seemed to be effective in providing cellular protection. However, large discrepancies are noted among several studies. For example, Sussan *et al*[44] have shown that double deletions of ApoE and Nrf2 genes in mice aortas showed a decrease in plaque area compared with ApoE knock-out mice in spite of the anti-oxidant effect of Nrf2. This suggests that upregulation of Nrf2 may play a detrimental role in generation of atherosclerosis. On the other hand, several studies have suggested beneficial roles of Nrf2 in the cardiovascular systems. These contradictory findings based on narrowly focused studies indicate that a broader understanding of Nrf2 is needed to understand the role of the oxidant/anti-oxidant system in cardiovascular disease. Physical activity and/or exercise training provides an ideal experimental context for further study of Nrf2 and other cytokines because acute exercise induces an increase in pro-inflammatory cytokine production that eventually stimulates anti-inflammatory

responses to achieve an overall beneficial anti-inflammatory effect. The elucidation of the mechanisms governing exercise-induced protection from disease in the cardiovascular system is needed to devise more effective therapies.

REFERENCES

1 **Kojda G**, Harrison D. Interactions between NO and reactive oxygen species: pathophysiological importance in atherosclerosis, hypertension, diabetes and heart failure. *Cardiovasc Res* 1999; **43**: 562-571
2 **Adams V**, Linke A, Kränkel N, Erbs S, Gielen S, Möbius-Winkler S, Gummert JF, Mohr FW, Schuler G, Hambrecht R. Impact of regular physical activity on the NAD(P)H oxidase and angiotensin receptor system in patients with coronary artery disease. *Circulation* 2005; **111**: 555-562
3 **Gao L**, Mann GE. Vascular NAD(P)H oxidase activation in diabetes: a double-edged sword in redox signalling. *Cardiovasc Res* 2009; **82**: 9-20
4 **Zhang Y**, Gordon GB. A strategy for cancer prevention: stimulation of the Nrf2-ARE signaling pathway. *Mol Cancer Ther* 2004; **3**: 885-893
5 **Surh YJ**, Kundu JK, Na HK. Nrf2 as a master redox switch in turning on the cellular signaling involved in the induction of cytoprotective genes by some chemopreventive phytochemicals. *Planta Med* 2008; **74**: 1526-1539
6 **Ungvari Z**, Parrado-Fernandez C, Csiszar A, de Cabo R. Mechanisms underlying caloric restriction and lifespan regulation: implications for vascular aging. *Circ Res* 2008; **102**: 519-528
7 **Lee JM**, Li J, Johnson DA, Stein TD, Kraft AD, Calkins MJ, Jakel RJ, Johnson JA. Nrf2, a multi-organ protector? *FASEB J* 2005; **19**: 1061-1066
8 **Mann GE**, Niehueser-Saran J, Watson A, Gao L, Ishii T, de Winter P, Siow RC. Nrf2/ARE regulated antioxidant gene expression in endothelial and smooth muscle cells in oxidative stress: implications for atherosclerosis and preeclampsia. *Shengli Xuebao* 2007; **59**: 117-127
9 **Motohashi H**, Yamamoto M. Nrf2-Keap1 defines a physiologically important stress response mechanism. *Trends Mol Med* 2004; **10**: 549-557
10 **Picchi A**, Gao X, Belmadani S, Potter BJ, Focardi M, Chilian WM, Zhang C. Tumor necrosis factor-alpha induces endothelial dysfunction in the prediabetic metabolic syndrome. *Circ Res* 2006; **99**: 69-77
11 **Gao X**, Belmadani S, Picchi A, Xu X, Potter BJ, Tewari-Singh N, Capobianco S, Chilian WM, Zhang C. Tumor necrosis factor-alpha induces endothelial dysfunction in Lepr(db) mice. *Circulation* 2007; **115**: 245-254
12 **Hallenbeck JM**. The many faces of tumor necrosis factor in stroke. *Nat Med* 2002; **8**: 1363-1368
13 **Hansson GK**. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005; **352**: 1685-1695
14 **Park Y**, Capobianco S, Gao X, Falck JR, Dellsperger KC, Zhang C. Role of EDHF in type 2 diabetes-induced endothelial dysfunction. *Am J Physiol Heart Circ Physiol* 2008; **295**: H1982-H1988
15 **Pajkrt D**, van der Poll T, Levi M, Cutler DL, Affrime MB, van den Ende A, ten Cate JW, van Deventer SJ. Interleukin-10 inhibits activation of coagulation and fibrinolysis during human endotoxemia. *Blood* 1997; **89**: 2701-2705
16 **Jankord R**, Jemiolo B. Influence of physical activity on serum IL-6 and IL-10 levels in healthy older men. *Med Sci Sports Exerc* 2004; **36**: 960-964
17 **Ouchi N**, Kihara S, Arita Y, Maeda K, Kuriyama H, Okamoto Y, Hotta K, Nishida M, Takahashi M, Nakamura T, Yamashita S, Funahashi T, Matsuzawa Y. Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. *Circulation* 1999; **100**: 2473-2476
18 **Ouchi N**, Kihara S, Arita Y, Okamoto Y, Maeda K, Kuriyama H, Hotta K, Nishida M, Takahashi M, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Funahashi T, Matsuzawa Y. Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kappaB signaling through a cAMP-dependent pathway. *Circulation* 2000; **102**: 1296-1301
19 **Albert MA**, Glynn RJ, Ridker PM. Effect of physical activity on serum C-reactive protein. *Am J Cardiol* 2004; **93**: 221-225
20 **Bruun JM**, Helge JW, Richelsen B, Stallknecht B. Diet and exercise reduce low-grade inflammation and macrophage infiltration in adipose tissue but not in skeletal muscle in severely obese subjects. *Am J Physiol Endocrinol Metab* 2006; **290**: E961-E967
21 **Flynn MG**, McFarlin BK, Markofski MM. State of the art reviews: The anti-inflammatory actions of exercise training. *Am J Lifestyle Med* 2007; **1**: 220-235
22 **Flynn MG**, McFarlin BK, Phillips MD, Stewart LK, Timmerman KL. Toll-like receptor 4 and CD14 mRNA expression are lower in resistive exercise-trained elderly women. *J Appl Physiol* 2003; **95**: 1833-1842
23 **Itoh K**, Wakabayashi N, Katoh Y, Ishii T, Igarashi K, Engel JD, Yamamoto M. Keap1 represses nuclear activation of antioxidant responsive elements by Nrf2 through binding to the amino-terminal Neh2 domain. *Genes Dev* 1999; **13**: 76-86
24 **Zhang DD**, Lo SC, Cross JV, Templeton DJ, Hannink M. Keap1 is a redox-regulated substrate adaptor protein for a Cul3-dependent ubiquitin ligase complex. *Mol Cell Biol* 2004; **24**: 10941-10953
25 **Cullinan SB**, Gordan JD, Jin J, Harper JW, Diehl JA. The Keap1-BTB protein is an adaptor that bridges Nrf2 to a Cul3-based E3 ligase: oxidative stress sensing by a Cul3-Keap1 ligase. *Mol Cell Biol* 2004; **24**: 8477-8486
26 **Kobayashi A**, Kang MI, Okawa H, Ohtsuji M, Zenke Y, Chiba T, Igarashi K, Yamamoto M. Oxidative stress sensor Keap1 functions as an adaptor for Cul3-based E3 ligase to regulate proteasomal degradation of Nrf2. *Mol Cell Biol* 2004; **24**: 7130-7139
27 **Nguyen T**, Sherratt PJ, Nioi P, Yang CS, Pickett CB. Nrf2 controls constitutive and inducible expression of ARE-driven genes through a dynamic pathway involving nucleocytoplasmic shuttling by Keap1. *J Biol Chem* 2005; **280**: 32485-32492
28 **Velichkova M**, Hasson T. Keap1 regulates the oxidation-sensitive shuttling of Nrf2 into and out of the nucleus via a Crm1-dependent nuclear export mechanism. *Mol Cell Biol* 2005; **25**: 4501-4513
29 **Sun Z**, Zhang S, Chan JY, Zhang DD. Keap1 controls postinduction repression of the Nrf2-mediated antioxidant response by escorting nuclear export of Nrf2. *Mol Cell Biol* 2007; **27**: 6334-6349
30 **He X**, Kan H, Cai L, Ma Q. Nrf2 is critical in defense against high glucose-induced oxidative damage in cardiomyocytes. *J Mol Cell Cardiol* 2009; **46**: 47-58
31 **Kobayashi M**, Yamamoto M. Nrf2-Keap1 regulation of cellular defense mechanisms against electrophiles and reactive oxygen species. *Adv Enzyme Regul* 2006; **46**: 113-140
32 **Zhang DD**. Mechanistic studies of the Nrf2-Keap1 signaling pathway. *Drug Metab Rev* 2006; **38**: 769-789
33 **Xue M**, Qian Q, Adaikalakoteswari A, Rabbani N, Babaei-Jadidi R, Thornalley PJ. Activation of NF-E2-related factor-2 reverses biochemical dysfunction of endothelial cells induced by hyperglycemia linked to vascular disease. *Diabetes* 2008; **57**: 2809-2817
34 **Balogun E**, Hoque M, Gong P, Killeen E, Green CJ, Foresti R, Alam J, Motterlini R. Curcumin activates the haem oxygenase-1 gene via regulation of Nrf2 and the antioxidant-responsive element. *Biochem J* 2003; **371**: 887-895
35 **Mukherjee S**, Gangopadhyay H, Das DK. Broccoli: a unique vegetable that protects mammalian hearts through the redox cycling of the thioredoxin superfamily. *J Agric Food Chem*

2008; **56**: 609-617
36 **Yeh CT**, Ching LC, Yen GC. Inducing gene expression of cardiac antioxidant enzymes by dietary phenolic acids in rats. *J Nutr Biochem* 2009; **20**: 163-171
37 **Matusheski NV**, Swarup R, Juvik JA, Mithen R, Bennett M, Jeffery EH. Epithiospecifier protein from broccoli (Brassica oleracea L. ssp. italica) inhibits formation of the anticancer agent sulforaphane. *J Agric Food Chem* 2006; **54**: 2069-2076
38 **Finley JW**. Reduction of cancer risk by consumption of selenium-enriched plants: enrichment of broccoli with selenium increases the anticarcinogenic properties of broccoli. *J Med Food* 2003; **6**: 19-26
39 **Dreger H**, Westphal K, Weller A, Baumann G, Stangl V, Meiners S, Stangl K. Nrf2-dependent upregulation of antioxidative enzymes: a novel pathway for proteasome inhibitor-mediated cardioprotection. *Cardiovasc Res* 2009; **83**: 354-361
40 **Naujokat C**, Hoffmann S. Role and function of the 26S proteasome in proliferation and apoptosis. *Lab Invest* 2002; **82**: 965-980
41 **Jesenberger V**, Jentsch S. Deadly encounter: ubiquitin meets apoptosis. *Nat Rev Mol Cell Biol* 2002; **3**: 112-121
42 **Elliott PJ**, Zollner TM, Boehncke WH. Proteasome inhibition: a new anti-inflammatory strategy. *J Mol Med* 2003; **81**: 235-245
43 **Calvert JW**, Jha S, Gundewar S, Elrod JW, Ramachandran A, Pattillo CB, Kevil CG, Lefer DJ. Hydrogen sulfide mediates cardioprotection through Nrf2 signaling. *Circ Res* 2009; **105**: 365-374
44 **Sussan TE**, Jun J, Thimmulappa R, Bedja D, Antero M, Gabrielson KL, Polotsky VY, Biswal S. Disruption of Nrf2, a key inducer of antioxidant defenses, attenuates ApoE-mediated atherosclerosis in mice. *PLoS One* 2008; **3**: e3791
45 **Manson JE**, Greenland P, LaCroix AZ, Stefanick ML, Mouton CP, Oberman A, Perri MG, Sheps DS, Pettinger MB, Siscovick DS. Walking compared with vigorous exercise for the prevention of cardiovascular events in women. *N Engl J Med* 2002; **347**: 716-725
46 **Niebauer J**, Hambrecht R, Velich T, Hauer K, Marburger C, Kälberer B, Weiss C, von Hodenberg E, Schlierf G, Schuler G, Zimmermann R, Kübler W. Attenuated progression of coronary artery disease after 6 years of multifactorial risk intervention: role of physical exercise. *Circulation* 1997; **96**: 2534-2541
47 **Lindström J**, Louheranta A, Mannelin M, Rastas M, Salminen V, Eriksson J, Uusitupa M, Tuomilehto J. The Finnish Diabetes Prevention Study (DPS): Lifestyle intervention and 3-year results on diet and physical activity. *Diabetes Care* 2003; **26**: 3230-3236
48 **Green DJ**, Maiorana A, O'Driscoll G, Taylor R. Effect of exercise training on endothelium-derived nitric oxide function in humans. *J Physiol* 2004; **561**: 1-25
49 **Wang J**, Wolin MS, Hintze TH. Chronic exercise enhances endothelium-mediated dilation of epicardial coronary artery in conscious dogs. *Circ Res* 1993; **73**: 829-838
50 **Fukai T**, Siegfried MR, Ushio-Fukai M, Cheng Y, Kojda G, Harrison DG. Regulation of the vascular extracellular superoxide dismutase by nitric oxide and exercise training. *J Clin Invest* 2000; **105**: 1631-1639
51 **Rush JW**, Turk JR, Laughlin MH. Exercise training regulates SOD-1 and oxidative stress in porcine aortic endothelium. *Am J Physiol Heart Circ Physiol* 2003; **284**: H1378-H1387
52 **Laughlin MH**, McAllister RM. Exercise training-induced coronary vascular adaptation. *J Appl Physiol* 1992; **73**: 2209-2225
53 **Trott DW**, Gunduz F, Laughlin MH, Woodman CR. Exercise training reverses age-related decrements in endothelium-dependent dilation in skeletal muscle feed arteries. *J Appl Physiol* 2009; **106**: 1925-1934
54 **Moien-Afshari F**, Ghosh S, Elmi S, Rahman MM, Sallam N, Khazaei M, Kieffer TJ, Brownsey RW, Laher I. Exercise restores endothelial function independently of weight loss or hyperglycaemic status in db/db mice. *Diabetologia* 2008; **51**: 1327-1337
55 **Moien-Afshari F**, Ghosh S, Elmi S, Khazaei M, Rahman MM, Sallam N, Laher I. Exercise restores coronary vascular function independent of myogenic tone or hyperglycemic status in db/db mice. *Am J Physiol Heart Circ Physiol* 2008; **295**: H1470-H1480
56 **Niess AM**, Passek F, Lorenz I, Schneider EM, Dickhuth HH, Northoff H, Fehrenbach E. Expression of the antioxidant stress protein heme oxygenase-1 (HO-1) in human leukocytes. *Free Radic Biol Med* 1999; **26**: 184-192
57 **Ostrowski K**, Hermann C, Bangash A, Schjerling P, Nielsen JN, Pedersen BK. A trauma-like elevation of plasma cytokines in humans in response to treadmill running. *J Physiol* 1998; **513** (Pt 3): 889-894
58 **Ostrowski K**, Rohde T, Asp S, Schjerling P, Pedersen BK. Pro- and anti-inflammatory cytokine balance in strenuous exercise in humans. *J Physiol* 1999; **515** (Pt 1): 287-291
59 **Zaldivar F**, Wang-Rodriguez J, Nemet D, Schwindt C, Galassetti P, Mills PJ, Wilson LD, Cooper DM. Constitutive pro- and anti-inflammatory cytokine and growth factor response to exercise in leukocytes. *J Appl Physiol* 2006; **100**: 1124-1133
60 **Nieman DC**, Henson DA, Smith LL, Utter AC, Vinci DM, Davis JM, Kaminsky DE, Shute M. Cytokine changes after a marathon race. *J Appl Physiol* 2001; **91**: 109-114
61 **Steensberg A**, Keller C, Starkie RL, Osada T, Febbraio MA, Pedersen BK. IL-6 and TNF-alpha expression in, and release from, contracting human skeletal muscle. *Am J Physiol Endocrinol Metab* 2002; **283**: E1272-E1278
62 **Febbraio MA**, Steensberg A, Starkie RL, McConell GK, Kingwell BA. Skeletal muscle interleukin-6 and tumor necrosis factor-alpha release in healthy subjects and patients with type 2 diabetes at rest and during exercise. *Metabolism* 2003; **52**: 939-944
63 **Drenth JP**, Van Uum SH, Van Deuren M, Pesman GJ, Van der Ven-Jongekrijg J, Van der Meer JW. Endurance run increases circulating IL-6 and IL-1ra but downregulates ex vivo TNF-alpha and IL-1 beta production. *J Appl Physiol* 1995; **79**: 1497-1503
64 **Rabinovich RA**, Figueras M, Ardite E, Carbó N, Troosters T, Filella X, Barberà JA, Fernandez-Checa JC, Argilés JM, Roca J. Increased tumour necrosis factor-alpha plasma levels during moderate-intensity exercise in COPD patients. *Eur Respir J* 2003; **21**: 789-794
65 **Febbraio MA**, Pedersen BK. Muscle-derived interleukin-6: mechanisms for activation and possible biological roles. *FASEB J* 2002; **16**: 1335-1347
66 **Petersen AM**, Pedersen BK. The anti-inflammatory effect of exercise. *J Appl Physiol* 2005; **98**: 1154-1162
67 **Fischer CP**, Hiscock NJ, Penkowa M, Basu S, Vessby B, Kallner A, Sjöberg LB, Pedersen BK. Supplementation with vitamins C and E inhibits the release of interleukin-6 from contracting human skeletal muscle. *J Physiol* 2004; **558**: 633-645
68 **Starkie R**, Ostrowski SR, Jauffred S, Febbraio M, Pedersen BK. Exercise and IL-6 infusion inhibit endotoxin-induced TNF-alpha production in humans. *FASEB J* 2003; **17**: 884-886
69 **Steensberg A**, Fischer CP, Keller C, Møller K, Pedersen BK. IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. *Am J Physiol Endocrinol Metab* 2003; **285**: E433-E437
70 **Pischon T**, Hankinson SE, Hotamisligil GS, Rifai N, Rimm EB. Leisure-time physical activity and reduced plasma levels of obesity-related inflammatory markers. *Obes Res* 2003; **11**: 1055-1064
71 **Panagiotakos DB**, Kokkinos P, Manios Y, Pitsavos C. Physical activity and markers of inflammation and thrombosis related to coronary heart disease. *Prev Cardiol* 2004; **7**: 190-194
72 **Colbert LH**, Visser M, Simonsick EM, Tracy RP, Newman AB, Kritchevsky SB, Pahor M, Taaffe DR, Brach J, Rubin S, Harris TB. Physical activity, exercise, and inflammatory markers in older adults: findings from the Health, Aging and Body Composition Study. *J Am Geriatr Soc* 2004; **52**: 1098-1104

73 **Smith JK**, Dykes R, Douglas JE, Krishnaswamy G, Berk S. Long-term exercise and atherogenic activity of blood mononuclear cells in persons at risk of developing ischemic heart disease. *JAMA* 1999; **281**: 1722-1727
74 **Gielen S**, Adams V, Möbius-Winkler S, Linke A, Erbs S, Yu J, Kempf W, Schubert A, Schuler G, Hambrecht R. Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. *J Am Coll Cardiol* 2003; **42**: 861-868
75 **Marcell TJ**, McAuley KA, Traustadóttir T, Reaven PD. Exercise training is not associated with improved levels of C-reactive protein or adiponectin. *Metabolism* 2005; **54**: 533-541
76 **Nassis GP**, Papantakou K, Skenderi K, Triandafillopoulou M, Kavouras SA, Yannakoulia M, Chrousos GP, Sidossis LS. Aerobic exercise training improves insulin sensitivity without changes in body weight, body fat, adiponectin, and inflammatory markers in overweight and obese girls. *Metabolism* 2005; **54**: 1472-1479
77 **Hammett CJ**, Oxenham HC, Baldi JC, Doughty RN, Ameratunga R, French JK, White HD, Stewart RA. Effect of six months' exercise training on C-reactive protein levels in healthy elderly subjects. *J Am Coll Cardiol* 2004; **44**: 2411-2413
78 **Nieman DC**. Immune response to heavy exertion. *J Appl Physiol* 1997; **82**: 1385-1394

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TOPIC HIGHLIGHT

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Endothelium-derived hyperpolarizing factor and diabetes

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Abstract

In addition to its role as a barrier between blood and tissues, the vascular endothelium is responsible for the synthesis and released of a number of vasodilators including prostaglandins, nitric oxide and endothelium-derived hyperpolarizing factor (EDHF). As one of these vasodilators, the specific nature of EDHF has not been fully elucidated, although a number of roles have been proposed. Importantly, many conditions, such as hypertension, hyperlipidemia, heart failure, ischemia-reperfusion and diabetes mellitus comprise vascular endothelial dysfunction with EDHF dysregulation. This article reviews reports on the role of EDHF in diabetes-related endothelial dysfunction.

Key words: Endothelial-dysfunction; Hyperglycemia; Potassium channels; Epoxyeicosatrienoic acids; Hydrogen peroxide

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INTRODUCTION

The endothelium consists of a single layer of cells lining the inner wall of the vasculature. It serves as a barrier between blood and tissues and actively participates in the regulation of vascular function. Vascular homeostasis and tone are controlled by the endothelium *via* the synthesis and release of a number of endothelial-derived relaxing and constricting substances. Under healthy conditions, the prevailing role of the endothelium is to release vasodilators, including the endothelium-derived relaxing factor (EDRF)[1], nitric oxide (NO)[2], prostacyclin (PGI2)[3] and endothelium-derived hyperpolarizing factor (EDHF)[4,5]. However, the balance or homeostasis between endothelial relaxing and constricting factors is disrupted in diseases such as hypertension, hyperlipidemia, heart failure, ischemia-reperfusion and diabetes mellitus. In the particular case of diabetes, it has been established that vascular dysfunction caused by impairment of endothelial-dependent vasodilation is present in various vascular beds of different animal models and humans. Several signaling pathways have been reported as underlying mechanisms responsible for the endothelial dysfunction associated with diabetic complications including the protein kinase C pathway, the polyol pathway, the pathway for formation and signaling

of advanced glycation end products and the hexosamine pathway[6]. Most studies on the mechanisms associated with vasodilation impairment in diabetes have focused on the role of NO and PGI2[7-9]. Recently, however, as the nature of EDHF and its ability to induce vasodilation is being revealed, EDHF is receiving increasing interest.

IDENTIFICATION AND CHARACTERIZATION OF EDHF

The first report concerning EDHF and its effects on smooth muscle cells can be traced back to over 20 years ago[10]. Since then, the nature of EDHF has been widely studied. However, even to this day, the very existence of EDHF remains obscure. In general, EDHF-mediated responses are considered to be endothelium-dependent relaxation responses that persist after blockade of PGI2 and NO synthesis (Figure 1)[11,12]. Although the chemical identification and functional characterization of EDHF appears to vary depending on vessel size, vascular bed and species studied, there are several major candidate molecules that, to varying extents, fulfill the criteria that would be expected of an EDHF. These molecules include: (1) The epoxyeicosatrienoic acids (EETs), which are metabolites of the arachidonic P450 epoxygenase pathway, which seem to account for a substantial portion of EDHF effects in a number of vascular beds[13,14], notably in the coronary circulation[15,16]; (2) The K^+ ions that are released from the endothelium through endothelial K-Ca channels[17,18]; (3) The electrical communications occurring through myoendothelial gap junctions that provide a pathway for the passage between endothelial and smooth muscle cells of small water-soluble molecules (< 1000 Da), such as cAMP, cGMP and Ca^{2+}, but not of proteins[19]; and (4) The H_2O_2 produced in the endothelium; as a catalase, a specific inhibitor of H_2O_2, it is able to inhibit mesenteric EDHF-mediated vascular relaxations and hyperpolarization in normal and more significantly in endothelial nitric oxide synthase (eNOS)$^{-/-}$ mice[20-23].

In relatively large vessels, such as the aorta and epicardial coronary arteries, NO has generally been considered the principal mediator of endothelial dependent relaxations[24-26]. This is supported by observations indicating there is no evidence for a contribution of EDHF to the endothelium-dependent relaxation observed in isolated rat aortic vessels[27]. In comparison, in small resistance vessels, including the human forearm microcirculation, it has become clear that EDHF is an important vasodilator and regulator of vascular tone and reactivity[11,26,28].

EDHF AND DIABETES

Diabetes-associated vascular complications constitute the most common clinical problem and the major cause of mortality in humans. Endothelial dysfunction is a key vascular complication in type 1 and type 2 diabetes, and is considered a major risk factor for life threatening cardiovascular events. Several mechanisms have been proposed to account for endothelial dysfunction and the increased risk of vascular disease in diabetes. These mechanisms include a reduced availability of substrate for the enzyme eNOS, an altered signal transduction pathway for the stimulation of vascular relaxation, an enhanced destruction of NO due to an increase in oxidative stress, and an increased release of endothelium-derived contracting factors that decrease the ability of smooth muscle to respond to EDRFs[29-33]. As mentioned above, EDHF is characterized by its leading to endothelial-dependent vasodilation *via* NO- and prostaglandin-independent mechanisms, particularly in resistance arteries where the contribution of NO appears to be less important than in conduit vessels, and where EDHF appears to play a major role in regulating tissue blood flow[4].

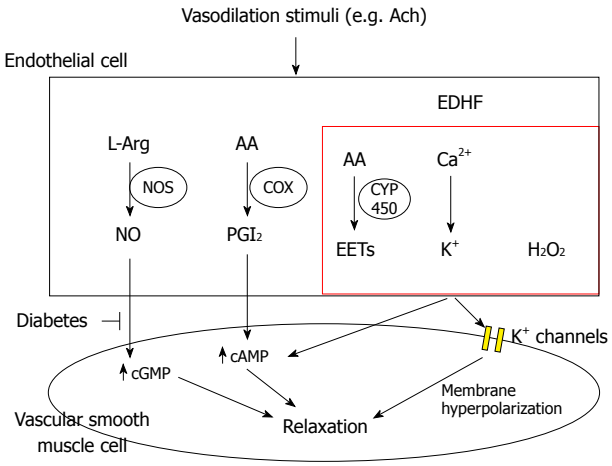

Figure 1 Endothelium-dependent vasodilation occurs in response to stimuli that induce the endothelial production and/or release of factors that ultimately cause the relaxation of the adjacent vascular smooth muscle. These factors include nitric oxide (NO), prostacyclin (PGI2), and endothelium-derived hyperpolarizing factor (EDHF). Depending on the species and vascular bed studied, the nature of the latter has been narrowed to include epoxyeicosatrienoic acids, K^+ ions, H_2O_2, and the myoendothelial junctions. In diabetes the presence of endothelial dysfunction is mostly characterized by a reduced bioavailability of NO. The effect of diabetes on EDHF is controversial, but a number of studies suggest that EDHF-dependent signaling may be increased therapeutically to ameliorate endothelial dysfunction. ACh: Acetylcholine; AA: Arachidonic acid; NOS: Nitric oxide synthase; COX: Cyclooxygenase; CYP 450: Cytochrome P450.

Insulino-dependent diabetes

Streptozotocin causes necrosis of β cells in the pancreas and is commonly used to induce type 1 diabetes in experimental animals. Type 1 diabetes is characterized by insulin deficiency compared to the insulin-resistance associated with type 2 diabetes. The exact role of EDHF in type 1 diabetes vascular dysfunction is not clear, but evidence suggests that there is both decreased and increased EDHF-mediated responses. A decrease in EDHF-mediated responses has been reported in mesenteric and carotid arteries as well as in the renal circulation of streptozotocin-treated diabetic rats[31,34-39]. The reduced EDHF-mediated response could be attributed to an increase in phospho-

diesterase-3 activity inducing a reduction in the action of cAMP[40]. This suggests that a selective phosphodiesterase inhibitor may improve EDHF-mediated responses in diabetes and that cAMP is partially involved in the EDHF-mediated relaxation, likely through the enhancement of electronic conduction *via* gap junctions[41,42]. In streptozotocin-treated diabetic rat models, there is a selective impairment of endothelium-dependent relaxation to acetylcholine in mesenteric arteries, but not in femoral arteries and this impairment is attributable to reduced EDHF-dependent rather than NO-dependent responses[43]. This again suggests that the EDHF-mediated response may be associated with vascular size and/or vascular beds. In streptozotocin-treated diabetic mice, EDHF-mediated relaxation is also weaker than in controls. However, the mRNA expression levels of putative EDHF components are unexpectedly increased in diabetic mesenteric arteries. Therefore, the EDHF-relaxation impairment may be, at least, in part, due to an increase in plasma low-density lipoprotein and/or lysophosphatidylcholine[44]. In apoE-deficient mice, streptozotocin also induces endothelial dysfunction associated with a reduced contribution of the EDHF component in acetylcholine-induced endothelial-dependent responses in small mesenteric arteries suggesting that an impairment in EDHF-dependent signaling may be conserved across species in Type 1 diabetes[45].

In contrast to the above reported results, an augmentation in EDHF-mediated relaxation was reported in femoral and mesenteric arteries of streptozotocin-treated animals[46]. This increase in EDHF-mediated vasodilation is believed to compensate for a reduced bioavailability of NO and to counteract the augmented endothelium-dependent vasoconstriction observed in these animals. This augmented relaxation mediated by EDHF, however, was not found in carotid arteries further illustrating the marked heterogeneity of endothelium-dependent responses in peripheral arteries of healthy rats and their deferential adaptation in the course of type 1 diabetes.

Non-insulino-dependent diabetes

Type 2 diabetes is characterized by insulin-resistance, hyperinsulinemia, moderate hyperglycemia and is often associated with hypertension. In animal models of type 2 diabetes, including the fructose-fed rat, the leptin-deficient, genetically obese and mildly hypertensive Zucker rat, and the Otsuka Long-Evans Tokushima Fatty (OLETF) rat, EDHF-mediated responses are inhibited with no or minor alterations in NO-dependent responses[47-51]. For example, in Zucker diabetic fatty rats relaxation to acetylcholine of sciatic nerve epineurial arterioles is impaired and this impairment is caused by a reduced acetylcholine-evoked relaxation mediated by the EDHF pathway[52,53]. There is also a report indicating that both EDHF-dependent hyperpolarization and relaxation and endothelium-independent relaxation are impaired in mesenteric arteries of Goto-Kakizaki rats (type 2 diabetic rat model), and that treatment with an AT1 receptor blocker failed to ameliorate the impaired EDHF-mediated responses[54].

In contrast, in db/db$^{-/-}$ mice, which have a mutation on the leptin receptor, the NO-mediated relaxation of mesenteric arteries is reduced, while the EDHF-mediated responses are preserved[55]. Whether these characteristics change when this animal model develops diabetes is controversial. However, a number of reports indicate that, while there is no change in the acetylcholine-induced contribution of EDHF to the relaxation responses of small mesenteric arteries from type 2 diabetic db/db mice, these vessels have a severe impairment in NO contribution to endothelium-dependent relaxation caused by a decrease bioavailability of NO without changes in eNOS protein levels[55-57]. Similarly in rabbits, where EDHF appears to act mainly through Ca^{2+}-activated K^+ channels, the EDHF-dependent contribution to endothelial dependent vasodilation in isolated renal arteries is not affected under diabetic conditions[58]. Cumulative evidence, thus, supports a role for an unchanged or augmented contribution of EDHF as a mechanism for maintaining endothelial dependent relaxation in type 2 diabetes and hyperlipidemic states when endothelial production of NO and prostaglandins are compromised, in particularly during the early stages of disease progression[59-62]. As for the mechanisms responsible for maintaining the EDHF response, there are multiple options. There are reports indicating that acetylcholine-induced EDHF-mediated relaxations in small mesenteric arteries in db/db mice involve Ca^{2+}-activated and inward rectifying K^+ channels as well as Na/K ATPase exchangers, but not EETs; conversely bradykinin-induced EDHF-dependent relaxations occur *via* cytochrome p450 products that activate large conductance Ca^{2+}-activated K^+ channels[45,55-57,63]. This indicates that the relative contribution of mediators/cellular pathways to the EDHF-mediated vasodilation to acetylcholine and bradykinin are both disease and agonist dependent.

Our own results indicate that endothelium-mediated vasodilation is primarily NO-dependent in coronary arterioles in wild-type mice[64]. However, we found that a portion of the NO-, endothelium-dependent vasodilation is significantly reduced in db/db mice, supporting the view that EDHF plays a pivotal role in type 2 diabetes-induced endothelial dysfunction[64]. We also found that in the coronary arterioles of wild-type mice three EDHF candidates, namely H_2O_2, K^+ and EETs, may play important roles in acetylcholine-induced endothelial-dependent vasodilation[64]. The impairment of the H_2O_2 response and/or the abnormalities in K^+ channels in advanced diabetes may be potential mechanisms for the reduction in EDHF-mediated vascular function in db/db mice. However, our studies suggest that the EETs are not involved in the endothelium-dependent, EDHF-mediated vasodilation in db/db mice. Furthermore, our findings support the concept that interleukin (IL)-6 plays a pivotal role in the EDHF-dependent endothelial dysfunction in type 2 diabetes, based on the observation that the presence of anti-IL-6-neutralizing antibody normalized coronary vascular function in diabetic db/db mice. Addition of IL-6 to the bath of wild type coronary vessels produced a similar degree

of dysfunction as that in the db/db mice, corroborating that IL-6 is an important contributor to vascular dysfunction in this animal model. At the molecular level we found that the expression of IL-6 was significantly increased in db/db mice[64]. Administration of an anti-IL-6 antibody attenuated IL-6 expression in db/db mice compared with wild type mice, while the expression of IL-6 was similar in diabetic mice null for tumor necrosis factor α (TNF-α) compared to wild type mice. Our findings, therefore, provide for a better understanding of the mechanisms that contribute to the role of EDHF in endothelial dysfunction at the level of the coronary microcirculation in type 2 diabetes. These findings also provide important new insights into the identity and mechanisms of EDHF-mediated vasodilation in the coronary circulation and may help identify novel therapeutic targets for the treatment of cardiovascular diseases associated with elevated levels of IL-6. EDHF contributes to endothelial-dependent vasodilation in maintaining coronary blood flow when the bioavailability of NO is substantially reduced in type 2 diabetes. Three EDHF candidates, K^+, EETs, and/or H_2O_2, are involved in the EDHF-mediated vasodilation in normal coronary circulation, but the EETs appear not to be involved in the diabetic condition. Studies investigating endothelial function in animal models of type 2 diabetes are still scarce and have yielded conflicting results. For each of the candidates for major contributors to EDHF-dependent signaling mentioned above there are both positive and negative reports on their involvement in diabetes-dependent endothelial dysfunction. While differences in diabetes model and in duration or severity of diabetes undoubtedly play a role in some of the discrepancies, difference in vascular bed, size of the vessel and conditions of the studies may be a much more important source of disparity.

EDHF AS A POTENTIAL TARGET IN THE TREATMENT OF DIABETES-ASSOCIATED ENDOTHELIAL DYSFUNCTION

Endothelial dysfunction in diabetes is primarily associated with a reduced bioavailability of endothelium-derived NO. However, as mentioned above, evidence indicates that EDHF, in a number of vascular beds, may act as a compensatory vasodilator in response to the reduced bioavailability of NO (Figure 1)[59,60]. This suggests that EDHF may be up-regulated despite the presence of the endothelial damage that reduces NO bioavailability. Due to the putative nature of EDHF, up-regulation of pathways that augment the conductivity of myoendothelial junctions support the hyperpolarization of endothelial cells, produce EETs, or maintain the vasodilatory effects of H_2O_2, may potentially be used to increase the production or effects of EDHF. However, only a small number of studies reporting significant therapeutically-induced changes in EDHF-related signaling in diabetes were originally aimed at manipulating EDHF; most were initially designed to affect NO-associated pathways, glucose, or lipid metabolism, but ultimately affected EDHF. Treatment for 4 wk with Metformin improved EDHF-mediated relaxation in mesenteric arteries isolated from the OLETF rat model of diabetes[65]. Metformin, is a biguanide used to treat diabetes primarily due to its antihyperglycemic properties, but its effects include cardiovascular protection *via* mechanisms independent of its glycemic effects[66,67]. Treatment with metformin also improved NO-dependent vascular relaxation in the OLEFT mesenteric arteries, and reduced the increased production of vasoconstrictor prostanoids that is associated with the diabetic state in that animal model[65]. Metformin, thus, appears to increase EDHF-mediated signaling through processes that improve overall endothelial function, and are likely related to a reduced production of derivatives of the cyclooxygenase pathway. In the same animal model (the OLETF rat), treatment with the selective phosphodiesterase 3 inhibitor, cilostazol, also increased EDHF-mediated vasodilation in mesenteric arteries without an improvement in endothelium derived NO-dependent responses[68]. In the OLETF rat model of diabetes, cAMP-dependent signaling is impaired, and in streptozotocin-treated animals, cilostazol improves cAMP-dependent signaling. Therefore, it has been suggested that cilostazol improves EDHF-dependent vasodilation in the OLETF rat by increasing cAMP-dependent signaling[68]. Matsumoto *et al*[69] also treated OLETF rats with eicosapentaenoic acid, an omega-3 polyunsaturated fatty acid, with the goal of ameliorating the endothelial dysfunction present in this animal model of diabetes. Treatment with eicosapentaenoic acid for 4 wk improved overall endothelial function in OLETF rats including an augmentation of EDHF- and NO-dependent vasodilations in mesenteric arteries. Importantly, eicosapentaenoic acid reduced nuclear factor κB activation and COX-2 expression, indicating that a reduced level of inflammation played a significant role in improving endothelial function.

A common treatment for patients with hypertension and diabetes consists of reducing the renin-angiotensin signaling pathway. In diabetic mice and rats, treatment with the angiotensin-Ⅱ receptor blockers, olmesartan or losartan, respectively, resulted in an overall amelioration of the endothelial dysfunction that included an increased relaxation response of mesenteric arteries to EDHF-dependent signaling[70-72]. In the Goto-Kakizaki rat model of diabetes, Losartan also improved EDHF-signaling, and this improvement was abolished by inhibition of the large conductance Ca^{2+}-activated K^+ channels (BK_{Ca}) with iberiotoxin[70]. Losartan also normalized the relaxation of mesenteric arteries occurring in response to activation of the small- (SK_{Ca}) and intermediate-conductance (IK_{Ca}) Ca^{2+}-activated K^+ channels, which are reduced in a number of rat models of diabetes[70,73]. It appears, however, that under "normal" conditions SK_{Ca} and IK_{Ca}, but not BK_{Ca} channels, are essential components of EDHF-signaling[11]. Thus, it remains to be fully determined if the roles of these channels in EDHF-dependent signaling change in disease states such as diabetes.

Overall, evidence indicates that treatments that ameliorate the endothelial dysfunction present in diabetes and reduce inflammatory signals in the endothelium improve EDHF dependent signaling. Recently, a study indicated that 1 mo of IL-6 treatment in rats with streptozotocin-induced diabetes resulted in an improved response to EDHF-dependent relaxation of isolated renal artery rings[74]. Treatment with IL-6 also improved a number the nerve functional parameters that are usually impaired in diabetes. These results appear divergent from our findings indicating that direct incubation of isolated coronary microvessels with IL-6 impairs EDHF-dependent relaxation in wild type mice, while blockade of IL-6 restores it in db/db diabetic mice[64]. This discrepancy may be related to the different models of diabetes used in the studies, the different vascular beds proved for the effects of IL-6 on EDHF-dependent signaling, and/or the time frame and characteristics of IL-6 treatment. Overall, however, evidence clearly indicates that inflammation and TNF-α dependent signaling are involved in the development of endothelial dysfunction in diabetes[75]. As TNF-α has been reported to augment the expression of IL-6[76,77], the role of IL-6 and its potential use as a target for reducing diabetes related vasculopathies needs further investigation.

CONCLUSION

Diabetes has become one of the most important risk factors for vascular disease and other syndromes associated with hyperglycemia that lead to increased mortality in humans. The endothelium plays an important role in the regulation of vascular tone, helping to maintain normal vascular function through the synthesis and release of several kinds of vasoactive factors, including NO, PGI2 and EDHF. Although diabetes is clearly associated with endothelial dysfunction characterized by a reduced bioavailability of NO, evidence for the role of EDHF in the vascular dysfunction present in diabetes is not clear. While EDHF-dependent signaling appears to compensate for the reduced bioavailability of NO in some vascular beds, in others it appears to be reduced. Part of this controversy is due to the variable nature of EDHF. Nonetheless evidence indicates that EDHF may be therapeutically manipulated in the diabetic state to ameliorate endothelial dysfunction and improve vascular performance. A better understanding of the relationship that exists between diabetes and EDHF should provide new insights for novel therapeutic targets to resolve the vascular diseases associated with diabetes.

REFERENCES

1 **Furchgott RF**, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. *Nature* 1980; **288**: 373-376
2 **Palmer RM**, Ferrige AG, Moncada S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature* 1987; **327**: 524-526
3 **Moncada S**, Gryglewski R, Bunting S, Vane JR. An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. *Nature* 1976; **263**: 663-665
4 **Garland CJ**, Plane F, Kemp BK, Cocks TM. Endothelium-dependent hyperpolarization: a role in the control of vascular tone. *Trends Pharmacol Sci* 1995; **16**: 23-30
5 **Komori K**, Vanhoutte PM. Endothelium-derived hyperpolarizing factor. *Blood Vessels* 1990; **27**: 238-245
6 **Brownlee M**. Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001; **414**: 813-820
7 **Taylor PD**, Graves JE, Poston L. Selective impairment of acetylcholine-mediated endothelium-dependent relaxation in isolated resistance arteries of the streptozotocin-induced diabetic rat. *Clin Sci* (Lond) 1995; **88**: 519-524
8 **Cai H**, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. *Circ Res* 2000; **87**: 840-844
9 **Calles-Escandon J**, Cipolla M. Diabetes and endothelial dysfunction: a clinical perspective. *Endocr Rev* 2001; **22**: 36-52
10 **Bolton TB**, Lang RJ, Takewaki T. Mechanisms of action of noradrenaline and carbachol on smooth muscle of guinea-pig anterior mesenteric artery. *J Physiol* 1984; **351**: 549-572
11 **Luksha L**, Agewall S, Kublickiene K. Endothelium-derived hyperpolarizing factor in vascular physiology and cardiovascular disease. *Atherosclerosis* 2009; **202**: 330-344
12 **Shimokawa H**. Hydrogen peroxide as an endothelium-derived hyperpolarizing factor. *Pflugers Arch* 2010; **459**: 915-922
13 **Mombouli JV**, Vanhoutte PM. Endothelium-derived hyperpolarizing factor(s): updating the unknown. *Trends Pharmacol Sci* 1997; **18**: 252-256
14 **Fisslthaler B**, Popp R, Kiss L, Potente M, Harder DR, Fleming I, Busse R. Cytochrome P450 2C is an EDHF synthase in coronary arteries. *Nature* 1999; **401**: 493-497
15 **Campbell WB**, Harder DR. Endothelium-derived hyperpolarizing factors and vascular cytochrome P450 metabolites of arachidonic acid in the regulation of tone. *Circ Res* 1999; **84**: 484-488
16 **Fleming I**. Cytochrome p450 and vascular homeostasis. *Circ Res* 2001; **89**: 753-762
17 **Edwards G**, Weston AH. Potassium and potassium clouds in endothelium-dependent hyperpolarizations. *Pharmacol Res* 2004; **49**: 535-541
18 **Edwards G**, Dora KA, Gardener MJ, Garland CJ, Weston AH. K+ is an endothelium-derived hyperpolarizing factor in rat arteries. *Nature* 1998; **396**: 269-272
19 **Griffith TM**, Chaytor AT, Edwards DH. The obligatory link: role of gap junctional communication in endothelium-dependent smooth muscle hyperpolarization. *Pharmacol Res* 2004; **49**: 551-564
20 **Matoba T**, Shimokawa H, Nakashima M, Hirakawa Y, Mukai Y, Hirano K, Kanaide H, Takeshita A. Hydrogen peroxide is an endothelium-derived hyperpolarizing factor in mice. *J Clin Invest* 2000; **106**: 1521-1530
21 **Matoba T**, Shimokawa H, Kubota H, Morikawa K, Fujiki T, Kunihiro I, Mukai Y, Hirakawa Y, Takeshita A. Hydrogen peroxide is an endothelium-derived hyperpolarizing factor in human mesenteric arteries. *Biochem Biophys Res Commun* 2002; **290**: 909-913
22 **Matoba T**, Shimokawa H, Morikawa K, Kubota H, Kunihiro I, Urakami-Harasawa L, Mukai Y, Hirakawa Y, Akaike T, Takeshita A. Electron spin resonance detection of hydrogen peroxide as an endothelium-derived hyperpolarizing factor in porcine coronary microvessels. *Arterioscler Thromb Vasc Biol* 2003; **23**: 1224-1230
23 **Yada T**, Shimokawa H, Hiramatsu O, Kajita T, Shigeto F, Goto M, Ogasawara Y, Kajiya F. Hydrogen peroxide, an endogenous endothelium-derived hyperpolarizing factor, plays an important role in coronary autoregulation in vivo. *Circulation* 2003; **107**: 1040-1045
24 **Shimokawa H**, Yasutake H, Fujii K, Owada MK, Nakaike R,

Fukumoto Y, Takayanagi T, Nagao T, Egashira K, Fujishima M, Takeshita A. The importance of the hyperpolarizing mechanism increases as the vessel size decreases in endothelium-dependent relaxations in rat mesenteric circulation. *J Cardiovasc Pharmacol* 1996; **28**: 703-711
25 **Busse R**, Edwards G, Félétou M, Fleming I, Vanhoutte PM, Weston AH. EDHF: bringing the concepts together. *Trends Pharmacol Sci* 2002; **23**: 374-380
26 **Inokuchi K**, Hirooka Y, Shimokawa H, Sakai K, Kishi T, Ito K, Kimura Y, Takeshita A. Role of endothelium-derived hyperpolarizing factor in human forearm circulation. *Hypertension* 2003; **42**: 919-924
27 **Endo K**, Abiru T, Machida H, Kasuya Y, Kamata K. Endothelium-derived hyperpolarizing factor does not contribute to the decrease in endothelium-dependent relaxation in the aorta of streptozotocin-induced diabetic rats. *Gen Pharmacol* 1995; **26**: 149-153
28 **Félétou M**, Vanhoutte PM. The alternative: EDHF. *J Mol Cell Cardiol* 1999; **31**: 15-22
29 **Harrison DG**. Cellular and molecular mechanisms of endothelial cell dysfunction. *J Clin Invest* 1997; **100**: 2153-2157
30 **Mombouli JV**, Vanhoutte PM. Endothelial dysfunction: from physiology to therapy. *J Mol Cell Cardiol* 1999; **31**: 61-74
31 **De Vriese AS**, Van de Voorde J, Blom HJ, Vanhoutte PM, Verbeke M, Lameire NH. The impaired renal vasodilator response attributed to endothelium-derived hyperpolarizing factor in streptozotocin--induced diabetic rats is restored by 5-methyltetrahydrofolate. *Diabetologia* 2000; **43**: 1116-1125
32 **Andrews KL**, Pannirselvam M, Anderson TJ, Jenkins AJ, Triggle CR, Hill MA. The vascular endothelium in diabetes: a practical target for drug treatment? *Expert Opin Ther Targets* 2005; **9**: 101-117
33 **Triggle CR**, Howarth A, Cheng ZJ, Ding H. Twenty-five years since the discovery of endothelium-derived relaxing factor (EDRF): does a dysfunctional endothelium contribute to the development of type 2 diabetes? *Can J Physiol Pharmacol* 2005; **83**: 681-700
34 **Fukao M**, Hattori Y, Kanno M, Sakuma I, Kitabatake A. Alterations in endothelium-dependent hyperpolarization and relaxation in mesenteric arteries from streptozotocin-induced diabetic rats. *Br J Pharmacol* 1997; **121**: 1383-1391
35 **Félétou M**, Vanhoutte PM. EDHF: new therapeutic targets? *Pharmacol Res* 2004; **49**: 565-580
36 **Kamata K**, Ohuchi K, Kirisawa H. Altered endothelium-dependent and -independent hyperpolarization and endothelium-dependent relaxation in carotid arteries isolated from streptozotocin-induced diabetic rats. *Naunyn Schmiedebergs Arch Pharmacol* 2000; **362**: 52-59
37 **Leo CH**, Hart JL, Woodman OL. Impairment of both nitric oxide-mediated and EDHF-type relaxation in small mesenteric arteries from rats with streptozotocin-induced diabetes. *Br J Pharmacol* 2011; **162**: 365-377
38 **Makino A**, Ohuchi K, Kamata K. Mechanisms underlying the attenuation of endothelium-dependent vasodilatation in the mesenteric arterial bed of the streptozotocin-induced diabetic rat. *Br J Pharmacol* 2000; **130**: 549-556
39 **Nakazawa T**, Kaneko Y, Mori A, Saito M, Sakamoto K, Nakahara T, Ishii K. Attenuation of nitric oxide- and prostaglandin-independent vasodilation of retinal arterioles induced by acetylcholine in streptozotocin-treated rats. *Vascul Pharmacol* 2007; **46**: 153-159
40 **Matsumoto T**, Kobayashi T, Kamata K. Alterations in EDHF-type relaxation and phosphodiesterase activity in mesenteric arteries from diabetic rats. *Am J Physiol Heart Circ Physiol* 2003; **285**: H283-H291
41 **Chaytor AT**, Taylor HJ, Griffith TM. Gap junction-dependent and -independent EDHF-type relaxations may involve smooth muscle cAMP accumulation. *Am J Physiol Heart Circ Physiol* 2002; **282**: H1548-H1555
42 **Griffith TM**, Chaytor AT, Taylor HJ, Giddings BD, Edwards DH. cAMP facilitates EDHF-type relaxations in conduit arteries by enhancing electrotonic conduction via gap junctions. *Proc Natl Acad Sci USA* 2002; **99**: 6392-6397
43 **Wigg SJ**, Tare M, Tonta MA, O'Brien RC, Meredith IT, Parkington HC. Comparison of effects of diabetes mellitus on an EDHF-dependent and an EDHF-independent artery. *Am J Physiol Heart Circ Physiol* 2001; **281**: H232-H240
44 **Matsumoto T**, Miyamori K, Kobayashi T, Kamata K. Specific impairment of endothelium-derived hyperpolarizing factor-type relaxation in mesenteric arteries from streptozotocin-induced diabetic mice. *Vascul Pharmacol* 2006; **44**: 450-460
45 **Ding H**, Hashem M, Wiehler WB, Lau W, Martin J, Reid J, Triggle C. Endothelial dysfunction in the streptozotocin-induced diabetic apoE-deficient mouse. *Br J Pharmacol* 2005; **146**: 1110-1118
46 **Shi Y**, Ku DD, Man RY, Vanhoutte PM. Augmented endothelium-derived hyperpolarizing factor-mediated relaxations attenuate endothelial dysfunction in femoral and mesenteric, but not in carotid arteries from type I diabetic rats. *J Pharmacol Exp Ther* 2006; **318**: 276-281
47 **Wu X**, Mäkynen H, Kähönen M, Arvola P, Pörsti I. Mesenteric arterial function in vitro in three models of experimental hypertension. *J Hypertens* 1996; **14**: 365-372
48 **Katakam PV**, Ujhelyi MR, Miller AW. EDHF-mediated relaxation is impaired in fructose-fed rats. *J Cardiovasc Pharmacol* 1999; **34**: 461-467
49 **Miller AW**, Katakam PV, Ujhelyi MR. Impaired endothelium-mediated relaxation in coronary arteries from insulin-resistant rats. *J Vasc Res* 1999; **36**: 385-392
50 **Kagota S**, Yamaguchi Y, Nakamura K, Kunitomo M. Altered endothelium-dependent responsiveness in the aortas and renal arteries of Otsuka Long-Evans Tokushima Fatty (OLETF) rats, a model of non-insulin-dependent diabetes mellitus. *Gen Pharmacol* 2000; **34**: 201-209
51 **Minami A**, Ishimura N, Harada N, Sakamoto S, Niwa Y, Nakaya Y. Exercise training improves acetylcholine-induced endothelium-dependent hyperpolarization in type 2 diabetic rats, Otsuka Long-Evans Tokushima fatty rats. *Atherosclerosis* 2002; **162**: 85-92
52 **Coppey LJ**, Gellett JS, Yorek MA. Mediation of vascular relaxation in epineurial arterioles of the sciatic nerve: effect of diabetes in type 1 and type 2 diabetic rat models. *Endothelium* 2003; **10**: 89-94
53 **Coppey LJ**, Gellett JS, Davidson EP, Dunlap JA, Yorek MA. Changes in endoneurial blood flow, motor nerve conduction velocity and vascular relaxation of epineurial arterioles of the sciatic nerve in ZDF-obese diabetic rats. *Diabetes Metab Res Rev* 2002; **18**: 49-56
54 **Oniki H**, Fujii K, Kansui Y, Goto K, Iida M. Effects of angiotensin II receptor antagonist on impaired endothelium-dependent and endothelium-independent relaxations in type II diabetic rats. *J Hypertens* 2006; **24**: 331-338
55 **Pannirselvam M**, Verma S, Anderson TJ, Triggle CR. Cellular basis of endothelial dysfunction in small mesenteric arteries from spontaneously diabetic (db/db -/-) mice: role of decreased tetrahydrobiopterin bioavailability. *Br J Pharmacol* 2002; **136**: 255-263
56 **Pannirselvam M**, Simon V, Verma S, Anderson T, Triggle CR. Chronic oral supplementation with sepiapterin prevents endothelial dysfunction and oxidative stress in small mesenteric arteries from diabetic (db/db) mice. *Br J Pharmacol* 2003; **140**: 701-706
57 **Pannirselvam M**, Wiehler WB, Anderson T, Triggle CR. Enhanced vascular reactivity of small mesenteric arteries from diabetic mice is associated with enhanced oxidative stress and cyclooxygenase products. *Br J Pharmacol* 2005; **144**: 953-960
58 **Yousif MH**, Cherian A, Oriowo MA. Endothelium-dependent relaxation in isolated renal arteries of diabetic rabbits. *Auton Autacoid Pharmacol* 2002; **22**: 73-82

59 **Krummen S**, Falck JR, Thorin E. Two distinct pathways account for EDHF-dependent dilatation in the gracilis artery of dyslipidaemic hApoB+/+ mice. *Br J Pharmacol* 2005; **145**: 264-270

60 **Krummen S**, Drouin A, Gendron ME, Falck JR, Thorin E. ROS-sensitive cytochrome P450 activity maintains endothelial dilatation in ageing but is transitory in dyslipidaemic mice. *Br J Pharmacol* 2006; **147**: 897-904

61 **Wölfle SE**, de Wit C. Intact endothelium-dependent dilation and conducted responses in resistance vessels of hypercholesterolemic mice in vivo. *J Vasc Res* 2005; **42**: 475-482

62 **Bełtowski J**, Wójcicka G, Jamroz-Wiśniewska A. Role of nitric oxide and endothelium-derived hyperpolarizing factor (EDHF) in the regulation of blood pressure by leptin in lean and obese rats. *Life Sci* 2006; **79**: 63-71

63 **Pannirselvam M**, Ding H, Anderson TJ, Triggle CR. Pharmacological characteristics of endothelium-derived hyperpolarizing factor-mediated relaxation of small mesenteric arteries from db/db mice. *Eur J Pharmacol* 2006; **551**: 98-107

64 **Park Y**, Capobianco S, Gao X, Falck JR, Dellsperger KC, Zhang C. Role of EDHF in type 2 diabetes-induced endothelial dysfunction. *Am J Physiol Heart Circ Physiol* 2008; **295**: H1982-H1988

65 **Matsumoto T**, Noguchi E, Ishida K, Kobayashi T, Yamada N, Kamata K. Metformin normalizes endothelial function by suppressing vasoconstrictor prostanoids in mesenteric arteries from OLETF rats, a model of type 2 diabetes. *Am J Physiol Heart Circ Physiol* 2008; **295**: H1165-H1176

66 **Knowler WC**, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346**: 393-403

67 **Anfossi G**, Russo I, Bonomo K, Trovati M. The cardiovascular effects of metformin: further reasons to consider an old drug as a cornerstone in the therapy of type 2 diabetes mellitus. *Curr Vasc Pharmacol* 2010; **8**: 327-337

68 **Matsumoto T**, Noguchi E, Ishida K, Nakayama N, Kobayashi T, Kamata K. Cilostazol improves endothelial dysfunction by increasing endothelium-derived hyperpolarizing factor response in mesenteric arteries from Type 2 diabetic rats. *Eur J Pharmacol* 2008; **599**: 102-109

69 **Matsumoto T**, Nakayama N, Ishida K, Kobayashi T, Kamata K. Eicosapentaenoic acid improves imbalance between vasodilator and vasoconstrictor actions of endothelium-derived factors in mesenteric arteries from rats at chronic stage of type 2 diabetes. *J Pharmacol Exp Ther* 2009; **329**: 324-334

70 **Matsumoto T**, Ishida K, Taguchi K, Kobayashi T, Kamata K. Losartan normalizes endothelium-derived hyperpolarizing factor-mediated relaxation by activating Ca2+-activated K+ channels in mesenteric artery from type 2 diabetic GK rat. *J Pharmacol Sci* 2010; **112**: 299-309

71 **Matsumoto T**, Ishida K, Nakayama N, Taguchi K, Kobayashi T, Kamata K. Mechanisms underlying the losartan treatment-induced improvement in the endothelial dysfunction seen in mesenteric arteries from type 2 diabetic rats. *Pharmacol Res* 2010; **62**: 271-281

72 **Hosoya M**, Ohashi J, Sawada A, Takaki A, Shimokawa H. Combination therapy with olmesartan and azelnidipine improves EDHF-mediated responses in diabetic apolipoprotein E-deficient mice. *Circ J* 2010; **74**: 798-806

73 **Brøndum E**, Kold-Petersen H, Simonsen U, Aalkjaer C. NS309 restores EDHF-type relaxation in mesenteric small arteries from type 2 diabetic ZDF rats. *Br J Pharmacol* 2010; **159**: 154-165

74 **Cotter MA**, Gibson TM, Nangle MR, Cameron NE. Effects of interleukin-6 treatment on neurovascular function, nerve perfusion and vascular endothelium in diabetic rats. *Diabetes Obes Metab* 2010; **12**: 689-699

75 **Zhang H**, Park Y, Wu J, Chen X, Lee S, Yang J, Dellsperger KC, Zhang C. Role of TNF-alpha in vascular dysfunction. *Clin Sci* (Lond) 2009; **116**: 219-230

76 **Turner NA**, Mughal RS, Warburton P, O'Regan DJ, Ball SG, Porter KE. Mechanism of TNFalpha-induced IL-1alpha, IL-1beta and IL-6 expression in human cardiac fibroblasts: effects of statins and thiazolidinediones. *Cardiovasc Res* 2007; **76**: 81-90

77 **Roher N**, Samokhvalov V, Díaz M, MacKenzie S, Klip A, Planas JV. The proinflammatory cytokine tumor necrosis factor-alpha increases the amount of glucose transporter-4 at the surface of muscle cells independently of changes in interleukin-6. *Endocrinology* 2008; **149**: 1880-1889

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REVIEW

Future easy and physiological cardiac pacing

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Abstract

The right atrial appendage (RAA) and right ventricular apex (RVA) have been widely considered as conventional sites for typical dual-chamber atrio-ventricular cardiac (DDD) pacing. Unfortunately conventional RAA pacing seems not to be able to prevent atrial fibrillation in DDD pacing for tachycardia-bradycardia syndrome, and the presence of a left bundle branch type of activation induced by RVA pacing can have negative effects. A new technology with active screw-in leads permits a more physiological atrial and right ventricular pacing. In this review, we highlight the positive effects of pacing of these new and easily selected sites. The septal atrial lead permits a shorter and more homogeneous atrial activation, allowing better prevention of paroxysmal atrial fibrillation. The para-Hisian pacing can be achieved in a simpler and more reliable way with respect to biventricular pacing and direct Hisian pacing. We await larger trials to consider this "easy and physiological pacing" as a first approach in patients who need a high frequency of pacing.

Key words: Cardiac pacing; Atrial septum; Parahisian pacing

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INTRODUCTION

Dual-chamber atrio-ventricular cardiac (DDD) pacing has produced clinical benefits with a considerable improvement in the symptoms and life expectancy of millions of patients suffering from chronic or paroxysmal disorders of cardiac electric excitation-conduction (atrio-ventricular block and/or sinus node disease).

Conventional sites for typical DDD pacing are the right atrial appendage (RAA) and the right ventricular apex (RVA), with well-known long-term safety and efficacy[1]. In the last few years some skepticism has emerged about pacing in both the RAA and RVA sites.

Papageorgiou *et al*[2] showed that during conventional RAA pacing, patients without a history of atrial arrhythmias but with inducible atrial fibrillation, exhibited a significant increase in conduction time of the posterior triangle of Koch and a marked broadening of the electrocardiogram recorded in this area. Saksena *et al*[3] reported that atrial fibrillation initiation was commonly associated with the appearance of an intra-atrial conduction delay of the initiating extra stimulus at the septal and coronary sinus ostial regions, and much less frequently at the crista terminalis. Thus, conventional RAA pacing does not seem to be able to prevent atrial fibrillation in DDD pacing for brady-tachi syndrome[4].

On the other hand, similar to the negative hemodynamic and clinical effects related to the presence of

spontaneous left bundle branch block, recent data suggest a possible negative effect associated with intraventricular conduction such as left bundle branch block induced by RVA pacing[5-9].

The negative effects of RVA pacing have been evaluated by some authors and could be summarized as: electric and mechanical left ventricular asynchrony; negative remodeling of the left ventricular chamber; alterations of the myocardial histopathology; systolic and diastolic left ventricular dysfunction; heart failure; regional myocardial and kinetic perfusion defects; functional mitral regurgitation; left atrial dilation; increased risk of atrial fibrillation; induction of spontaneous ventricular arrhythmias; and hyperactivation of the sympathetic nervous system.

Several studies have shown the negative clinical consequences caused by RVA pacing, including CTOPP[10], a Danish study[11], DAVID[12], MOST[13], and a substudy of MADIT II[14]. In all these trials, when the percentage of RVA pacing, obtained from the conventional apical site, was high (> 40%), the incidence of atrial fibrillation increased, along with heart failure, hospitalization and even death.

These negative effects appear more in patients with impairment of left ventricular systolic function, but not so much in patients without left ventricular systolic dysfunction before pacing. In particular, these effects do not seem to be predictive parameters for identifying patients with a higher risk of a long-term detrimental outcome related to RVA pacing.

In our study[15], we evaluated 33 patients treated with RVA pacing frequently for 2 years and showed: (1) a significant decrease in left ventricular ejection fraction (from 56% ± 6% to 43% ± 9%, $P < 0.001$); (2) an increase in left the ventricular volumes (telediastolic from 98 ± 22 to 139 ± 31 mL, $P < 0.001$; telesystolic from 43 ± 12 to 80 ± 22 mL, $P < 0.001$); (3) an increase in mitral valve regurgitation (semi-quantitative index from 0.8 ± 0.68 to 1.45 ± 0.93, $P < 0.001$); and (4) a worsening of NYHA class (from 1.15 ± 0.36 to 1.88 ± 0.99, $P < 0.05$).

We also observed a reduction in quality of life (Minnesota score) between the study and control group (score 29 ± 18 *vs* 21 ± 13, $P < 0.06$) and in a 6-min walking test (338 ± 158 m *vs* 448 ± 110 m, $P < 0.05$)

In the control group of 22 patients treated with a permanent pacemaker but with a very low frequency of RVA pacing, we did not find statistically significant differences, either echocardiographically or clinically, between pre-implantation and follow-up parameters.

ALTERNATIVE SITES OF ATRIAL PACING

Inter- and intra-atrial conduction delay due to RAA pacing is associated with a high incidence of atrial fibrillation. Thus in patients affected by sick sinus syndrome alternative sites of atrial pacing have been tested. The principal methods were: (1) biatrial pacing[16] achieved by a pacing system that ensured permanent biatrial pacing using two atrial leads, one placed in the high right atrium and the other in the mid or the distal part of the coronary sinus; (2) dual right atrial pacing[17] achieved by a simultaneous pacing at the high right atrium (conventional site in the atria) and coronary sinus ostium; and (3) interatrial septum pacing at the triangle of Koch achieved by a single lead placed superiorly and posteriorly at the coronary sinus ostium[18].

The main benefits that these sites should provide are: (1) a very short interatrial conduction delay and a significant decrease in P-wave duration; (2) a reduction in dispersion of atrial refractoriness; (3) a more homogeneous recovery of excitability and atrial activation; and (4) electrical atrial remodeling, with a gradual reduction in left atrial diameters and volume.

Data on the two lead techniques (dual site atrial pacing or biatrial pacing) are still controversial[19-21]. In contrast, the single lead interatrial septum pacing seems to be easier, and more effective and feasible, compared with conventional RAA pacing, providing significant benefits in preventing paroxysmal atrial fibrillation and decreasing the progression to chronic atrial fibrillation[18,22].

Thus, in patients with sinus bradycardia and paroxysmal atrial fibrillation, interatrial single lead septal pacing should be considered as the gold standard technique for permanent atrial pacing.

Recently, in the South European and South American Select Secure Registry, interatrial septal pacing was safely achieved in 125 patients using a new catheter (Select Secure 3830, Medtronic Inc., Minneapolis, Minnesota), applied at the pacing site from the outside through a steerable introducer (Select Site, Medtronic Inc., Minneapolis, Minnesota)[23].

ALTERNATIVE SITES OF VENTRICULAR PACING

Based on the results of various clinical studies, it is clear that a physiologic pacing modality should preserve a correct atrio-ventricular activation in order to achieve physiological ventricular synchronization.

The simplest way to avoid right ventricular pacing is atrial single chamber pacing in patients with intact atrio-ventricular and intraventricular conduction[24]. This solution, however, has seldom been applied because of the unjustified fear of late atrio-ventricular block. An alternative solution could be to implant a DDD device with an atrial and a ventricular lead, using a dedicated algorithm that limits RVA pacing as much as possible[25].

When permanent ventricular pacing is necessary, physiologic pacing sites should be used in order to prevent ventricular desynchronization[26]. This can be obtained through biventricular pacing or pacing from alternative sites of the right ventricle.

In addition to the important randomized trials evaluating cardiac resynchronization therapy (COMPANION[27], CARE-HF[28], MADIT-CRT[29], REVERSE[30]) that showed functional improvement and higher survival rates in patients with refractory heart failure and left bundle branch

block, various studies were performed in order to compare biventricular pacing and conventional RVA pacing. These studies have shown how resynchronization therapy leads to an improvement in hemodynamic parameters and systolic functioning, a reduction in mitral regurgitation and diameter of the left ventricle, and a reduction in the activity of the sympathetic nervous system[31-34]. Recently, Yu *et al*[35] documented a positive effect of biventricular pacing *vs* conventional RVA pacing in patients with normal left ventricular function needing permanent ventricular pacing.

The right ventricular outflow tract (RVOT) has been evaluated as a potential alternative site of ventricular pacing[36]. In a metaanalysis of nine prospective, but not randomized studies, de Cock *et al*[37] demonstrated an improvement in hemodynamic parameters achieved by RVOT pacing compared with conventional RVA pacing. However, the ROVA study, the only randomized study comparing RVOT with RVA pacing, gave disappointing results on the quality of life[38].

A further evolution of RVOT pacing is contemporaneous bifocal pacing of the apex and RVOT[39]; even in this case, however, the results are still controversial[40].

DIRECT HIS BUNDLE PACING AND PARA-HISIAN PACING

In 2000, Deshmukh *et al*[41] presented a case history of patients with permanent pacing of the bundle of His, documenting the reliability and effectiveness of this type of pacing after ablation of the atrio-ventricular junction (12/18 patients with chronic atrial fibrillation, left ventricular ejection fraction < 40% and QRS < 120 ms). In 2004, the same author[42] presented a wider study in a population of 54 patients suffering from dilated cardiomyopathy, with ejection fraction 23 ± 11%, persistent atrial fibrillation and QRS < 120 ms, in which direct pacing of the His bundle was achieved in 36/54 patients (66%): after a follow-up of 42 mo, 29 patients were still alive and an improvement in the ejection fraction and clinical and hemodynamic parameters of the left ventricle was obtained.

The parameters that allow for the direct pacing of the His bundle are: (1) the morphology and the duration of the native QRS and the paced QRS must be identical on the 12 standard ECG derivations (Figure 1: a patient in our study); (2) the HV interval on the original rhythm and the spike-QRS distance in the paced signal must be equal (with a tolerance margin of 10 ms); (3) the pacing threshold must be high (> 2 V), since it must capture specific non-muscular conduction tissue; and (4) the pacing lead should be positioned with the distal pole (screw in) at the same level as one of the two electrodes of a mapping catheter on the His bundle (in X-rays in both right and left anterior oblique projections) (Figure 2: a patient in our study).

Other authors have also assessed the feasibility and effectiveness of permanent Hisian pacing. Recently, Zanon *et al*[43] published a study showing how direct His bundle pacing can be obtained in a more reliable way using a new catheter (Select Secure 3830, Medtronic Inc., Minneapolis, Minnesota) applied at the pacing site from the outside through a steerable introducer (Select Site, Medtronic Inc., Minneapolis, Minnesota). The results showed that in 24 of 26 patients a direct stable pacing of the His bundle was obtained. The time needed to reach the His bundle with the permanent catheter varied from 2 to 60 min, with 3.8 ± 2.5 attempts required. The acute pacing threshold was 2.3 ± 1 V (0.5 ms) and the endocardial detected potential was 2.9 ± 2 mV.

These studies have shown that permanent pacing of the His bundle is a reliable and effective method preventing the desynchronization and negative effects of RVA pacing. It remains, however, a complex methodology requiring longer average implant times and presenting high pacing thresholds. Hisian pacing is also affected by the theoretical risk of His bundle block induced by the trauma and injury caused by the catheter screw-in lead[44]. In addition, due to the possible progression of conduction system disease, a right apical back-up pacing lead, avoiding future problems related to a high pacing threshold and/or a conduction block below the Hisian pacing site, could be necessary.

Para-Hisian pacing (PHP), which is simpler and more reliable, seems to guarantee physiological ventricular activation of the high muscular part of the intraventricular septum, and also early invasion of the His-Purkinje conduction system, very similar to the activation that can be achieved by direct His bundle pacing[45].

Recently, Laske *et al*[46] assessed left ventricular activation in pigs during pacing from various zones of the interventricular septum. During intrinsic activation with pacing from the right atrium, the activation spread along the septum and rapidly reached the left apical ventricular region, continued along the lateral wall and finally reached the postero-lateral region. Even during pacing from the para-Hisian region, the activation was the same as the intrinsic activation: it originated from the high septum and from the posterior region of the left ventricle, and then activated the anterior wall, the septum and the left ventricular apex.

From September 2000 to December 2009, at the Cardiology Clinic of the "Maggiore della Carità" Hospital, University of Eastern Piedmont, Novara, Italy, 135 patients underwent permanent right ventricular pacing in the Hisian/para-Hisian region (85 males, 50 females; 74 ± 8 years aged). In 92 patients we used a conventional screw-in lead, and in 43 patients the fixed screw was a 4 French lead (Select Secure 3830, Medtronic Inc., Minneapolis, Minnesota).

The correct criteria for the realization of para-Hisian pacing were[47]: (1) the distal pole of the catheter (screw-in) must be positioned as much as possible next to the mapping dipole of the electrophysiological catheter of reference (within 1 cm in the right and left oblique projections) (Figure 3: a patient in our study); (2) the duration of the

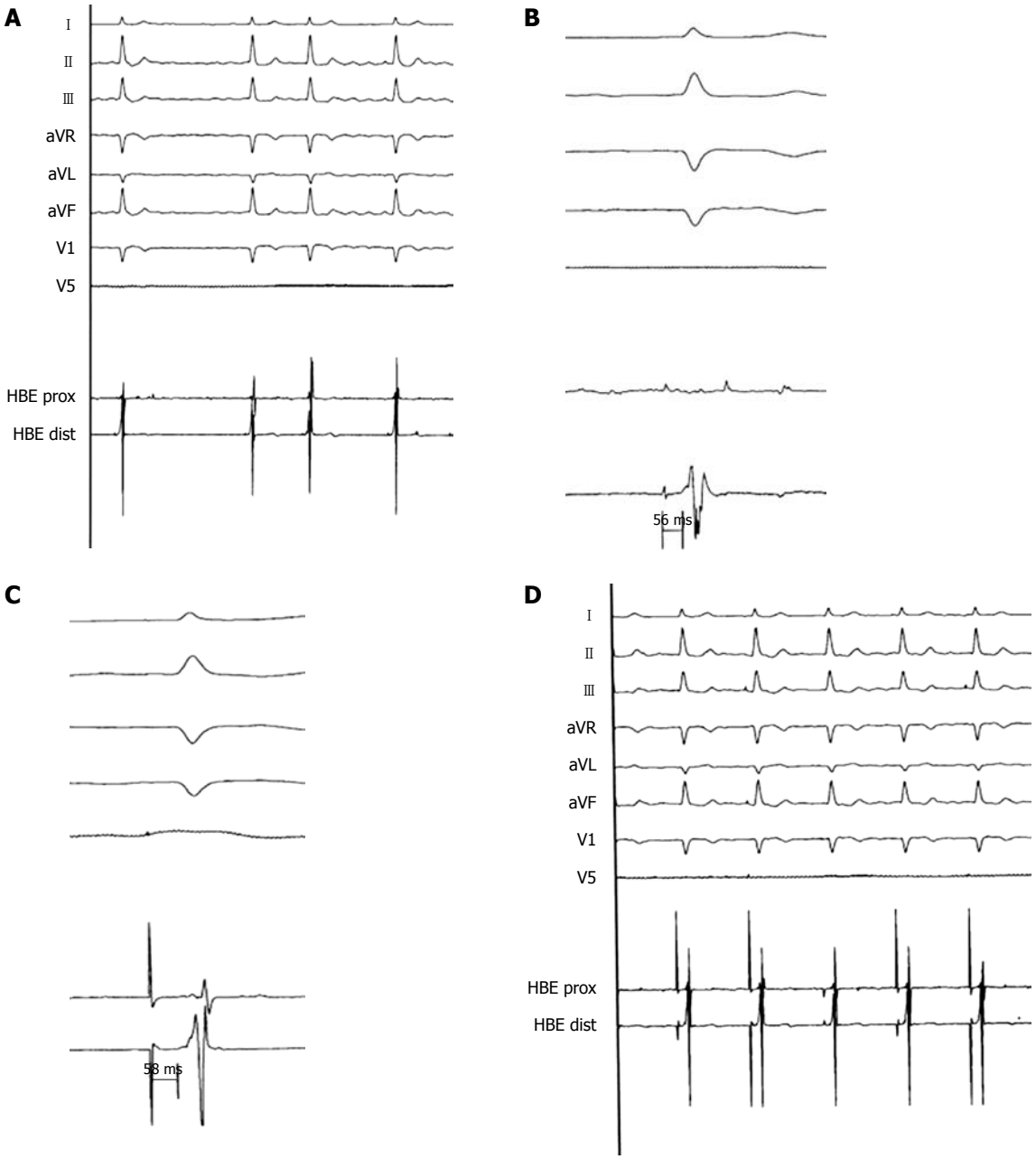

Figure 1 Spontaneous and Hisian paced ECGs. A: Surface electrocardiogram (ECG; peripheral derivations and V1-V5) and endocardial electrogram (EGM; His bundle site) during chronic atrial fibrillation: the QRS is narrow (90 ms) (registration speed 25 mm/s); B: His bundle registration: HV 56 ms (registration speed 50 mm/s); C: Spike-V during direct Hisian pacing equal to the basal HV (58 ms) (registration speed 100 mm/s); D: Surface ECG (peripheral derivations and V1-V5) and endocardial EGM (His bundle site) during direct Hisian pacing: the QRS is equal to the native QRS (registration speed 25 mm/s).

paced QRS can be larger than the spontaneous QRS, but the duration must be at least 50 ms shorter than the QRS obtained with RVA pacing and, in any case, not more than 120-130 ms (Figure 4: a patient in our study); (3) the electrical axis of the paced QRS must be concordant with the electrical axis of the spontaneous QRS; (4) the interval between the spike and start of the paced QRS is less than the HV interval of the original rhythm; and (5) the pacing threshold must be less than 1 V, since the muscular portion of the interventricular septum is paced.

Before the pacing (basal conditions) and during the follow-up all patients underwent: (1) NYHA class evaluation; (2) a quality of life questionnaire (Minnesota Living Heart Failure score); (3) a 6-min walking test; and (4) echocardiographic transthoracic standard evaluation (left ventricular end diastolic and end systolic volumes with consequent ejection fraction) and mitral and tricuspidal regurgitation semiquantitative scoring.

The pacing threshold from the Hisian site varied from 3.8 V in case of direct Hisian pacing (obtained in 20/135 patients: 15%), to values of always < 1 V in case of para-Hisian pacing (in 115/135 patients: 85%). The average duration of the basal QRS was 97.9 ± 12.4 ms, of QRS by para-Hisian pacing 123.9 ± 10.6 ms.

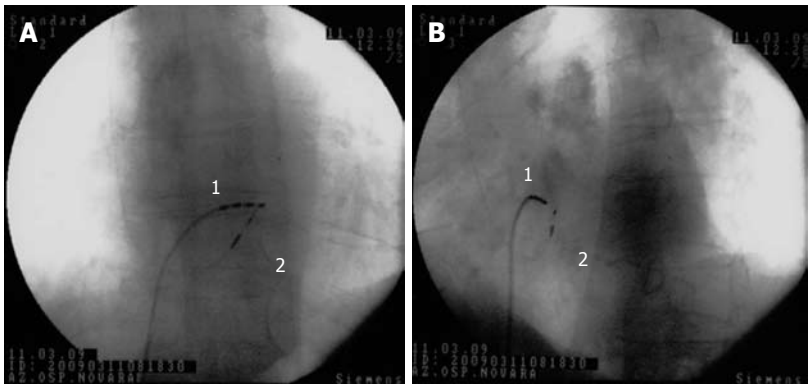

Figure 2 His bundle pacing. Antero-posterior (A) and left anterior oblique (B) fluoroscopic projections showing the screw-in lead (Select Secure, Medtronic) position during the procedure for a direct His bundle pacing; 1 = quadripolar Hisian mapping catheter; 2 = screw-in bipolar lead positioned in close proximity to the His bundle.

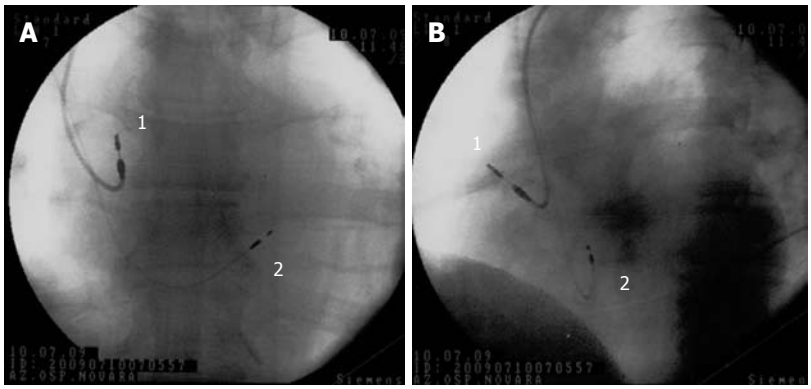

Figure 3 Para-Hisian pacing. Antero-posterior (A) and left anterior oblique (B) fluoroscopic projections showing lead positions after dual-chamber atrio-ventricular cardiac para-Hisian pacing. 1 = conventional screw-in atrial lead, placed into the right atrium; 2 = screw-in bipolar lead (Select Secure, Medtronic) positioned near the His bundle.

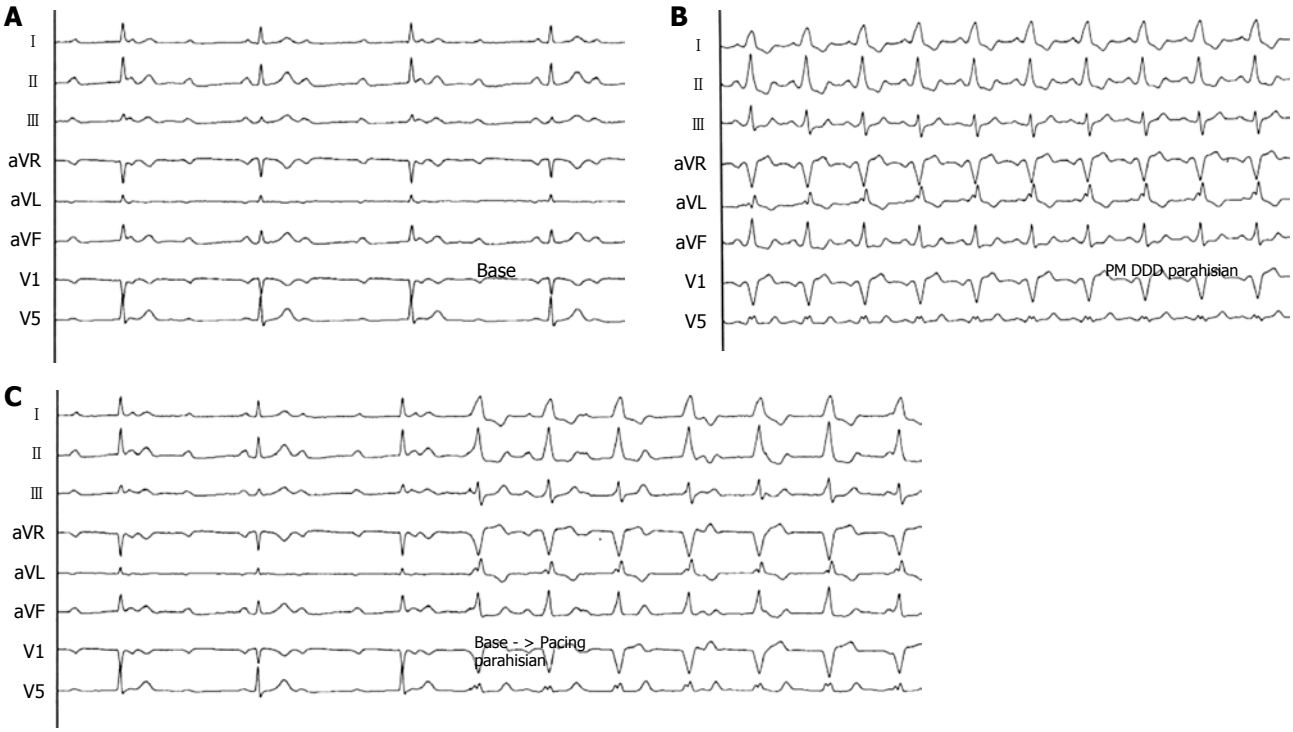

Figure 4 Spontaneous and para-Hisian paced ECGs. A: Surface ECG (peripheral derivations and V1-V5) during complete AV block with narrow QRS (90 ms) (registration speed 25 mm/s); B: Surface ECG (peripheral derivations and V1-V5) during para-Hisian pacing: the QRS is larger respect to the native QRS (registration speed 25 mm/s); C: Passage from to the native QRS to the para-Hisian paced QRS: the electrical axis is exactly the same (registration speed 25 mm/s). DDD: Dual-chamber atrio-ventricular cardiac pacing.

The mean follow-up of our patients is currently 27 mo, ranging from 103 mo for the first patient enrolled to 3 mo for the last patient. In the medium to long-term follow-up, patients with para-Hisian pacing showed the same QRS duration as the value recorded at the implant. The pacing threshold in Hisian/para-Hisian region did not have any

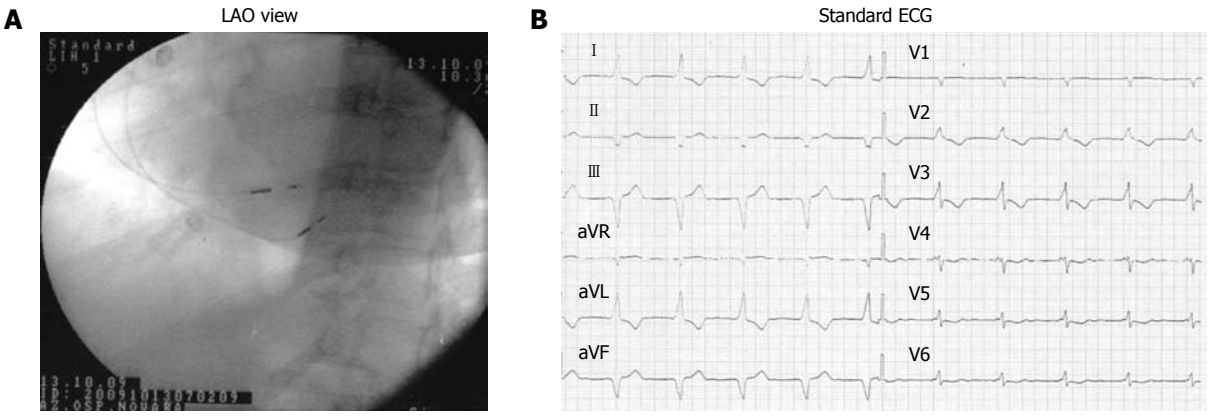

Figure 5 Atrial septal and para-Hisian dual-chamber atrio-ventricular cardiac pacing. A: left anterior oblique (LAO) fluoroscopic projections showing atrial septal lead and para-Hisian ventricular lead positions; B: 12-lead surface ECG during dual-chamber atrio-ventricular cardiac septal pacing (atrial septal lead and para-Hisian ventricular lead).

significant variations, with values remaining within acceptable safety margins.

A significant improvement in clinical outcomes was obtained with Hisian/para-Hisian pacing: NYHA functional class from 2.2 ± 0.5 to 1.5 ± 0.6; exercise tolerance (6 min walk) from 349 ± 100 to 400 ± 88 m; quality of life score from 28 ± 18 to 19 ± 16; mitral regurgitation score from 1.6 ± 0.8 to 1.1 ± 0.8 and tricuspid regurgitation score from 1.4 ± 0.9 to 1.2 ± 0.8. The mean ejection fraction showed a slight impairment (from 52% ± 11% before pacemaker implantation to 48% ± 12% in the follow-up), but with absolute values always above 40%-45%; this fact confirms that the Hisian/para-Hisian pacing can prevent deterioration of left ventricular function.

Our data showed that a selective right ventricular pacing, which is more physiological that RVA pacing, could prevent some detrimental effects on left ventricular function achieving a better clinical outcome. Other authors documented a preservation of coronary perfusion[48] and ventricular synchronization[49] with Hisian pacing compared with RVA pacing. Obviously, at present, we do not know if the Hisian/para-Hisian pacing could prevent all the negative effects of RVA pacing, discussed in the Introduction. Dedicated and larger studies should evaluate and confirm the physiopathological (dyssynchronia, atrial and ventricular remodeling, myocardial histopathology, regional myocardial perfusion, hyperactivation of the sympathetic nervous system) and clinical (heart failure, increased risk of atrial fibrillation, spontaneous ventricular arrhythmias, *etc.*) effects.

FINAL CONSIDERATIONS

The main purpose of permanent cardiac electrostimulation is to maintain an adequate cardiac rhythm, and restore the physiology of the normal excitatory-conductive physiology of the heart as much as possible. Until now, importance had been given to two elements considered crucial for physiological pacing: maintenance of the atrio-ventricular sequence and the rate-responsive function. Pacemakers, therefore, were considered "physiological".

Today and in the future, a truly physiological pacing, must: (1) maintain the correct stimulation-contraction sequence in the right and left atria; (2) maintain the synchrony between right and left ventricles; (3) maintain the sequence between the atria and ventricles; and (4) help increase the cardiac rate according to metabolic need.

We can identify three categories of patient requiring permanent cardiac pacing: (1) patients with paroxysmal excitation and/or conduction diseases: in this kind of patient, atrial and ventricular leads could be placed at conventional sites (RAA and RVA), because of the need for a very low rate of pacing. Current algorithms that decrease the frequency of ventricular pacing (e.g. SafeR, Sorin Group, Italy; MVP, Medtronic, USA; AV search hysteresis) could also be used in these situations; (2) patients with left ventricular dysfunction and electro-mechanical desynchronization indexes (QRS > 120 ms and/or echocardiographic asynchrony): these patients should have resynchronization therapy (CRT) with biventricular pacing (atrial, right and left ventricular leads); and (3) patients needing permanent atrial and/or ventricular pacing, with electric intraventricular conduction preserved (QRS < 120 ms): in these patients the optimal physiological pacing should be performed with: (1) an atrial lead actively fixed on the inter atrial septum (at the triangle of Koch site); and (2) a ventricular lead actively fixed at the para-Hisian region (Figure 5). The recently proposed biventricular pacing also in these patients[35] could be too invasive and expensive, and not even indicated in all patients.

The septal atrial lead permits a shorter and more homogeneous atrial activation, allowing better prevention of paroxysmal atrial fibrillation. Para-Hisian pacing can be obtained in a simpler and more reliable way, and is easier to perform compared with biventricular pacing and also the direct Hisian pacing. In this case, the high muscular part of the intraventricular septum is activated, while at the same time the Hisian conduction axis is penetrated, with a rather narrow QRS (120-130 ms) and with the electric axis concordant with the non-paced spontaneous QRS.

We await larger trials to consider this method of "easy

and physiological pacing" as a first approach in patients who require a high frequency of pacing.

REFERENCES

1 **Barold SS**. Modern cardiac pacing. Mount Kisco, New York: Futura Publishing Co., 1985
2 **Papageorgiou P**, Monahan K, Boyle NG, Seifert MJ, Beswick P, Zebede J, Epstein LM, Josephson ME. Site-dependent intra-atrial conduction delay. Relationship to initiation of atrial fibrillation. *Circulation* 1996; **94**: 384-389
3 **Saksena S**, Giorgberidze I, Prakash A, Hill M, Krol R, Munsif A, Mathew P, Mehra R. Endocardial mapping during induced atrial fibrillation (abstract). *Circulation* 1996; 94 (Suppl 1): I-555
4 **Feuer JM**, Shandling AH, Messenger JC. Influence of cardiac pacing mode on the long-term development of atrial fibrillation. *Am J Cardiol* 1989; **64**: 1376-1379
5 **Barold SS**. Adverse effects of ventricular desynchronization induced by long-term right ventricular pacing. *J Am Coll Cardiol* 2003; 42: 624-626
6 **Prinzen FW**, Peschar M. Relation between the pacing induced sequence of activation and left ventricular pump function in animals. *Pacing Clin Electrophysiol* 2002; **25**: 484-498
7 **Tantengco MV**, Thomas RL, Karpawich PP: Left ventricular dysfunction after long- term right ventricular apical pacing in the young. *J Am Coll Cardiol* 2001; 37: 2093-2100
8 **Karpawich PP**, Rabah R, Haas JE. Altered cardiac histology following apical right ventricular pacing in patients with congenital atrioventricular block. *Pacing Clin Electrophysiol* 1999; **22**: 1372-1377
9 **Tse HF**, Yu C, Wong KK, Tsang V, Leung YL, Ho WY, Lau CP. Functional abnormalities in patients with permanent right ventricular pacing: the effect of sites of electrical stimulation. *J Am Coll Cardiol* 2002; **40**: 1451-1458
10 **Connolly SJ**, Kerr CR, Gent M, Roberts RS, Yusuf S, Gillis AM, Sami MH, Talajic M, Tang AS, Klein GJ, Lau C, Newman DM. Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. Canadian Trial of Physiologic Pacing Investigators. *N Engl J Med* 2000; **342**: 1385-1391
11 **Nielsen JC**, Kristensen L, Andersen HR, Mortensen PT, Pedersen OL, Pedersen AK. A randomized comparison of atrial and dual-chamber pacing in 177 consecutive patients with sick sinus syndrome: echocardiographic and clinical outcome. *J Am Coll Cardiol* 2003; **42**: 614-623
12 **Wilkoff BL**, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H, Kutalek SP, Sharma A. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. *JAMA* 2002; **288**: 3115-3123
13 **Sweeney MO**, Hellkamp AS, Ellenbogen KA, Greenspon AJ, Freedman RA, Lee KL, Lamas GA. Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. *Circulation* 2003; **107**: 2932-2937
14 **Goldenberg I**, Moss AJ, Hall WJ, McNitt S, Zareba W, Andrews ML, Cannom DS. Causes and consequences of heart failure after prophylactic implantation of a defibrillator in the multicenter automatic defibrillator implantation trial II. *Circulation* 2006; **113**: 2810-2817
15 **Occhetta E**, Nappo R, Francalacci G, Bortnik M, Marino P. Left ventricular dysfunction induced by right ventricular apical pacing in patients with normal left ventricular function: incidence and quantification after 2 years follow up (abstract). *Europace* 2008; **10** (Suppl 1): 128
16 **Daubert C**, Mabo P, Berder V, Gras D, Leclercq C. Atrial tachyarrhythmias associated with a high degree of interatrial conduction block: prevention by permanent atrial resynchronization. *Eur J Card Pac Electrophysiol* 1994; **4**: 35-44
17 **Saksena S**, Prakash A, Hill M, Krol RB, Munsif AN, Mathew PP, Mehra R. Prevention of recurrent atrial fibrillation with chronic dual-site right atrial pacing. *J Am Coll Cardiol* 1996; **28**: 687-694
18 **Padeletti L**, Pieragnoli P, Ciapetti C, Colella A, Musilli N, Porciani MC, Ricci R, Pignalberi C, Santini M, Puglisi A, Azzolini P, Spampinato A, Martelli M, Capucci A, Boriani G, Botto G, Proclemer A. Randomized crossover comparison of right atrial appendage pacing versus interatrial septum pacing for prevention of paroxysmal atrial fibrillation in patients with sinus bradycardia. *Am Heart J* 2001; **142**: 1047-1055
19 **Delfaut P**, Saksena S, Prakash A, Krol RB. Long-term outcome of patients with drug-refractory atrial flutter and fibrillation after single- and dual-site right atrial pacing for arrhythmia prevention. *J Am Coll Cardiol* 1998; **32**: 1900-1908
20 **Anselme F**, Saoudi N, Cribier A. Pacing in prevention of atrial fibrillation: the PIPAF studies. *J Interv Card Electrophysiol* 2000; **4** Suppl 1: 177-184
21 **Saksena S**, Prakash A, Ziegler P, Hummel JD, Friedman P, Plumb VJ, Wyse DG, Johnson E, Fitts S, Mehra R. Improved suppression of recurrent atrial fibrillation with dual-site right atrial pacing and antiarrhythmic drug therapy. *J Am Coll Cardiol* 2002; **40**: 1140-1150; discussion 1151-1152
22 **Padeletti L**, Pürerfellner H, Adler SW, Waller TJ, Harvey M, Horvitz L, Holbrook R, Kempen K, Mugglin A, Hettrick DA. Combined efficacy of atrial septal lead placement and atrial pacing algorithms for prevention of paroxysmal atrial tachyarrhythmia. *J Cardiovasc Electrophysiol* 2003; **14**: 1189-1195
23 **Sagone A**, Lombardo E, Svetlich C, Padeletti L, D'Aurelio M, Dalbon C, Marotta T, Senatore G. Atrial pacing in selective site with select secure system: feasibility of implant and mid term follow-up electrical data (abstract). XIII World Congress on Cardiac pacing and Electrophysiology. *GIAC* 2007; **10**: 3
24 **Andersen HR**, Thuesen L, Bagger JP, Vesterlund T, Thomsen PE. Prospective randomised trial of atrial versus ventricular pacing in sick-sinus syndrome. *Lancet* 1994; **344**: 1523-1528
25 **Sweeney MO**, Ellenbogen KA, Casavant D, Betzold R, Sheldon T, Tang F, Mueller M, Lingle J. Multicenter, prospective, randomized safety and efficacy study of a new atrial-based managed ventricular pacing mode (MVP) in dual chamber ICDs. *J Cardiovasc Electrophysiol* 2005; **16**: 811-817
26 **Manolis AS**. The deleterious consequences of right ventricular apical pacing: time to seek alternate site pacing. *Pacing Clin Electrophysiol* 2006; **29**: 298-315
27 **Bristow MR**, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004; **350**: 2140-2150
28 **Cleland JG**, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005; 352: 1539-1549
29 **Moss AJ**, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009; **361**: 1329-1338
30 **Linde C**, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol* 2008; **52**: 1834-1843
31 **Hamdan MH**, Zagrodzky JD, Joglar JA, Sheehan CJ, Ramaswamy K, Erdner JF, Page RL, Smith ML. Biventricular pacing decreases sympathetic activity compared with right ventricular pacing in patients with depressed ejection fraction. *Circulation* 2000; **102**: 1027-1032

32 **Yu CM**, Lin H, Fung WH, Zhang Q, Kong SL, Sanderson JE. Comparison of acute changes in left ventricular volume, systolic and diastolic functions, and intraventricular synchronicity after biventricular and right ventricular pacing for heart failure. *Am Heart J* 2003; **145**: E18

33 **Doshi RN**, Daoud EG, Fellows C, Turk K, Duran A, Hamdan MH, Pires LA. Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). *J Cardiovasc Electrophysiol* 2005; **16**: 1160-1165

34 **Kindermann M**, Hennen B, Jung J, Geisel J, Böhm M, Fröhlig G. Biventricular versus conventional right ventricular stimulation for patients with standard pacing indication and left ventricular dysfunction: the Homburg Biventricular Pacing Evaluation (HOBIPACE). *J Am Coll Cardiol* 2006; **47**: 1927-1937

35 **Yu CM**, Chan JY, Zhang Q, Omar R, Yip GW, Hussin A, Fang F, Lam KH, Chan HC, Fung JW. Biventricular pacing in patients with bradycardia and normal ejection fraction. *N Engl J Med* 2009; **361**: 2123-2134

36 **Lieberman R**, Grenz D, Mond HG, Gammage MD. Selective site pacing: defining and reaching the selected site. *Pacing Clin Electrophysiol* 2004; **27**: 883-886

37 **de Cock CC**, Giudici MC, Twisk JW. Comparison of the haemodynamic effects of right ventricular outflow-tract pacing with right ventricular apex pacing: a quantitative review. *Europace* 2003; **5**: 275-278

38 **Res JC**, Bokern MJ, Vos DH. Characteristics of bifocal pacing: right ventricular apex versus outflow tract. An interim analysis. *Pacing Clin Electrophysiol* 2005; **28** Suppl 1: S36-S38

39 **Pachón JC**, Pachón EI, Albornoz RN, Pachón JC, Kormann DS, Gimenes VM, Medeiros PT, Silva MA, Sousa JE, Paulista PP, Souza LC, Jatene AD. Ventricular endocardial right bifocal stimulation in the treatment of severe dilated cardiomyopathy heart failure with wide QRS. *Pacing Clin Electrophysiol* 2001; **24**: 1369-1376

40 **Barold SS**, Audoglio R, Ravazzi PA, Diotallevi P. Is bifocal right ventricular pacing a viable form of cardiac resynchronization? *Pacing Clin Electrophysiol* 2008; **31**: 789-794

41 **Deshmukh P**, Casavant DA, Romanyshyn M, Anderson K. Permanent, direct His-bundle pacing: a novel approach to cardiac pacing in patients with normal His-Purkinje activation. *Circulation* 2000; **101**: 869-877

42 **Deshmukh PM**, Romanyshyn M. Direct His-bundle pacing: present and future. *Pacing Clin Electrophysiol* 2004; **27**: 862-870

43 **Zanon F**, Baracca E, Aggio S, Pastore G, Boaretto G, Cardano P, Marotta T, Rigatelli G, Galasso M, Carraro M, Zonzin P. A feasible approach for direct his-bundle pacing using a new steerable catheter to facilitate precise lead placement. *J Cardiovasc Electrophysiol* 2006; **17**: 29-33

44 **Amitani S**, Miyahara K, Sohara H, Kakura H, Koga M, Moriyama Y, Taira A, Nagano S, Miura N, Misumi K, Sakamoto H. Experimental His-bundle pacing: histopathological and electrophysiological examination. *Pacing Clin Electrophysiol* 1999; **22**: 562-566

45 **Occhetta E**, Bortnik M, Magnani A, Francalacci G, Piccinino C, Plebani L, Marino P. Prevention of ventricular desynchronization by permanent para-Hisian pacing after atrioventricular node ablation in chronic atrial fibrillation: a crossover, blinded, randomized study versus apical right ventricular pacing. *J Am Coll Cardiol* 2006; **47**: 1938-1945

46 **Laske TG**, Skadsberg ND, Hill AJ, Klein GJ, Iaizzo PA. Excitation of the intrinsic conduction system through his and interventricular septal pacing. *Indian Pacing Electrophysiol J* 2006; **29**: 397-405

47 **Occhetta E**, Bortnik M, Marino P. Permanent parahisian pacing. *Indian Pacing Electrophysiol J* 2006; **7**: 110-125

48 **Zanon F**, Bacchiega E, Rampin L, Aggio S, Baracca E, Pastore G, Marotta T, Corbucci G, Roncon L, Rubello D, Prinzen FW. Direct His bundle pacing preserves coronary perfusion compared with right ventricular apical pacing: a prospective, cross-over mid-term study. *Europace* 2008; **10**: 580-587

49 **Catanzariti D**, Maines M, Cemin C, Broso G, Marotta T, Vergara G. Permanent direct his bundle pacing does not induce ventricular dyssynchrony unlike conventional right ventricular apical pacing. An intrapatient acute comparison study. *J Interv Card Electrophysiol* 2006; **16**: 81-92

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CASE REPORT

Central obesity, hypertension and coronary artery disease: The seed and soil hypothesis

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Abstract

Coronary artery disease (CAD) is a multifactorial disease wherein hereditary and environmental factors play a major role. Our hypothesis is that an individual's genetic profile functions as soil while various environmental factors such as physical inactivity, smoking, stress etc. act as seeds in the etiopathogenesis of CAD. Much of the information regarding genetic and environmental factors can be determined in a pedigree chart by taking a history of the index patient, including details of major risk factors such as age, sex, smoking, hypertension, diabetes, coronary artery disease and stroke in the family. Preparing such a chart is a cost-effective way of initiating primary preventive measures in patients in a developing economy. The advantage of a detailed pedigree chart is to provide a snapshot view of the evident and underlying risk factors in the family as a whole, and not to merely study conventional risk factors. It elucidates the hidden stressors and hereditary factors responsible for cardiovascular disease in the family. We report herein an illustrative pedigree chart which exemplifies our above hypothesis.

INTRODUCTION

Coronary artery disease (CAD) is a multifactorial disease wherein hereditary and environmental factors play a major role. Our hypothesis is that an individual's genetic profile functions as soil while various environmental factors such as physical inactivity, smoking, stress etc. act as seeds in the etiopathogenesis of CAD. Much of the information regarding genetic and environmental factors can be determined in a pedigree chart by taking a history of the index patient, including details of major risk factors such as age, sex, smoking, hypertension, diabetes, coronary artery disease and stroke in the family[1]. Preparing such a chart is a cost-effective way of initiating primary preventive measures in patients in a developing economy. We report herein an illustrative pedigree chart which exemplifies our above hypothesis.

We had the opportunity to observe and assess three generations of a family over a period of 15 years. We collected information by verbal interview[2] of individuals and made detailed cardiovascular assessments in both parents of the index case, in 8 of his siblings and in one child of

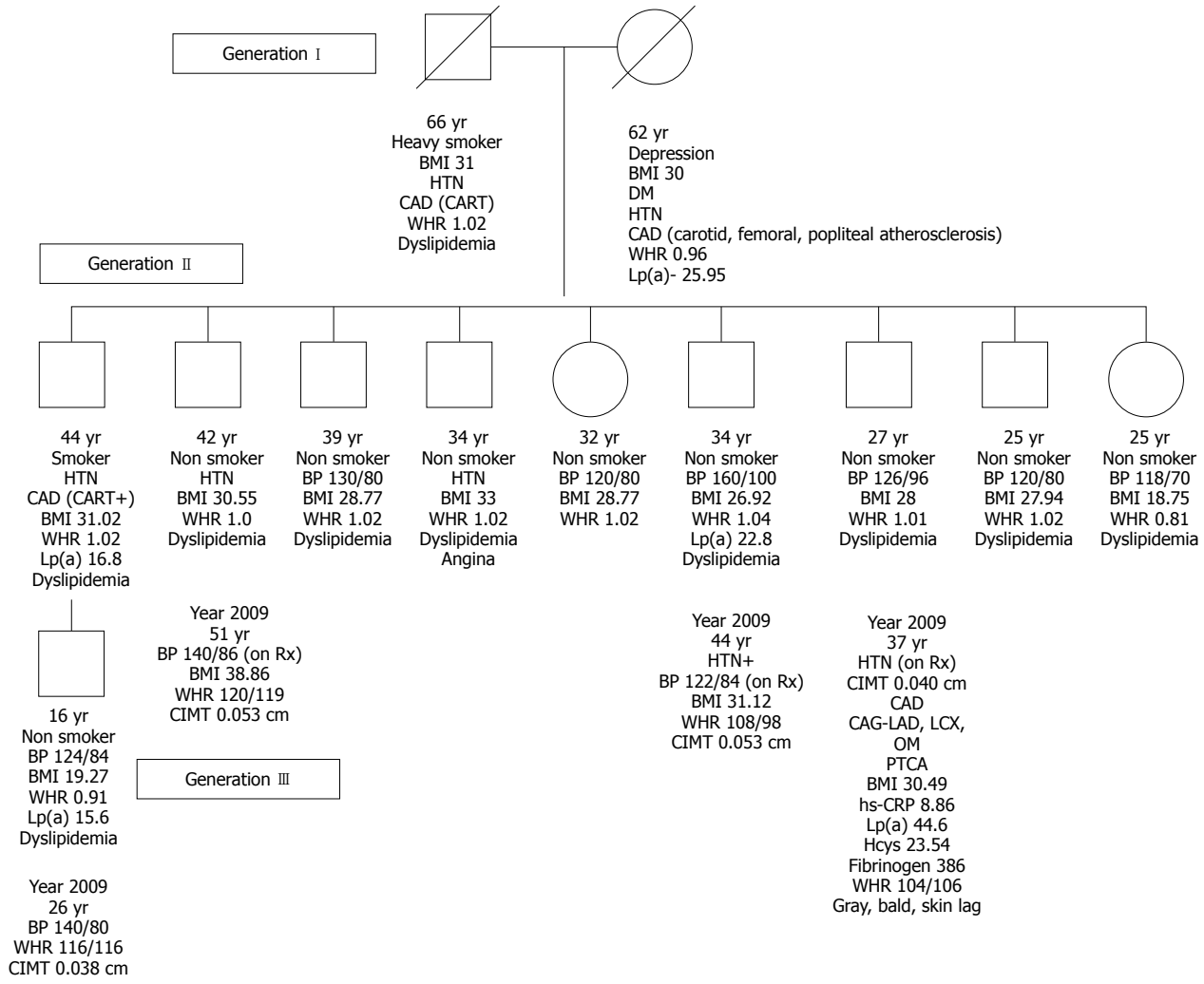

Figure 1 Pedigree chart corroborating the "seed and soil" hypothesis. Effect of environmental factors such as smoking on the eldest child, physical inactivity manifesting as central obesity in all due to a sedentary lifestyle in the second generation culminating in various sequelae of metabolic syndrome and prehypertension evolving into hypertension in the third generation. BMI: Body mass index; BP: Blood pressure; CAD: Coronary artery disease; CAG: Coronary angiography; CART: Coronary arteriography; CIMT: Carotid intima media thickness; DM: Diabetes mellitus; Dyslip: Dyslipidemia; HTN: Hypertension; Lp(a): Lipoprotein (a); TVD: Triple vessel disease; WHR: Waist hip ratio.

the index patient in the third generation. Thus a total of 12 members were examined and assessed in detail (Figure 1). Three of the siblings and the child were again assessed after 10 years. Primary preventive measures were initiated in the second generation and the effect on smoking, physical activity and diet were assessed over the years.

CASE REPORT

Initially, the 66-year-old father of the index patient presented with acute myocardial infarction. He was a chronic heavy smoker and a known hypertensive; he had manifest central obesity and dyslipidemia. A few months later, the 62-year-old mother, a known diabetic for 10 years with diabetic triopathy i.e. nephropathy, retinopathy and neuropathy, was admitted to hospital with acute thrombotic stroke and myocardial infarction. She too was obese and hypertensive. The fact that both parents suffered from CAD prematurely and had multiple cardiovascular risk factors, led us to prepare a pedigree chart of the entire family.

It was interesting to find that even with a single high risk behavior like smoking, the eldest son of the second generation (the index patient) had developed frank CAD at a young age (44 years). This also provided us with a tool to emphasize to the entire family that they should not smoke, which fortunately was followed strictly by the siblings and progeny of the eldest son. However, the advice regarding physical activity, morning walks and a healthy diet was not followed strictly and regularly.

The son of the index patient in the third generation passed through a phase of prehypertension and, 10 years later, had developed hypertension as well as central obesity. He is thus at risk of future CAD. Another sibling of the index case had to undergo coronary revascularization at the age of 37. He had a sedentary lifestyle, central obesity and hypertension. The role of hereditary factors in this family is so obvious that we can see that children in

the second and third generations have a high prevalence of risk factors, namely central obesity, hypertension, dyslipidemia and CAD, at a much earlier age compared with the first generation parents. The explanation for the high prevalence of central obesity and hypertension in the family is that the entire family was engaged in a sedentary business with no place for any physical activity and shared a common food habit with a high fat and salt content.

Limitations of the present report are that it pertains to a single family over the years and thus the number of patients is limited.

DISCUSSION

The advantage of preparing such a detailed pedigree chart is to prepare a snapshot view of the evident and underlying risk factors in the family as a whole, and not to merely study conventional risk factors. It elucidates the hidden stressors and hereditary factors responsible for cardiovascular disease in the family. Making such a comprehensive chart provides a definite basis for initiating primary preventive measures in high risk siblings and progeny of the affected patients at the earliest opportunity[3]. We did succeed in persuading the second and third generation subjects not to smoke on the basis of this chart; however much more emphatic measures are needed to implement dietary and exercise reforms in the family. Preparing a pedigree chart of this kind is obviously a cost-effective way of detecting prospective high risk individuals thus tackling the rising trend of cardiovascular disease in a developing economy.

REFERENCES

1 **Dwivedi S**, Awasthy N. Familial aggregation of coronary risk. *South Asian J Prev Cardiol* 1993; **3**: 60-63
2 **Chandramohan D**, Maude GH, Rodrigues LC, Hayes RJ. Verbal autopsies for adult deaths: issues in their development and validation. *Int J Epidemiol* 1994; **23**: 213-222
3 **Dwivedi S**, Agarwal MP, Suthar CP, Dwivedi G. Migration accelerates development of metabolic syndrome--an interesting pedigree. *Indian Heart J* 2004; **56**: 258-259

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Meetings

Events Calendar 2011

January 25
Moving towards a national strategy for Chronic Obstructive Pulmonary Disease
London, United Kingdom

Februrary 24-26
Abdominal Obesity 2011 - 2nd International Congress on Abdominal Obesity
Buenos Aires, Argentina

Februrary 25-27
CardioRhythm 2011
Hong Kong, China

March 19-26
Cardiology Update: Caribbean Cruise
San Diego, CA, United States

March 25
Cardiology for General Practice
London, United Kingdom

April 1-2
11th Annual Spring Meeting on Cardiovascular Nursing
Brussels, Belgium

April 14-16
EuroPRevent 2011
Genova, Switzerland

April 30-May 4
ATC 2011 - 2011 American Transplant Congress
Philadelphia, United States

May 11-14
3th Radiochemotherapy and Brachitherapy Congress & 6th Medical Physycs Meeting
Córdoba, Argentina

May 15-18
ICNC10 - Nuclear Cardiology and Cardiac CT
Amstedan, The Netherlands

May 19-20
Adult Cardiovascular Pathology
London, United Kingdom

May 20-22
XXIX NATIONAL CARDIOLOGY CONGRESS
Córdoba, Argentina

May 20-22
4th Meeting Uremic Toxins and Cardiovascular Disease
Groningen, The Netherlands

May 21-24
Heart Failure Congress 2011
Gothenburg, Sweden

June 2-5
CODHy 2011 - The 1st Asia Pacific Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension
Shanghai, China

June 26-29
EHRA EUROPACE 2011
Madrid, Spain

June 29-July 1
Hands-on Cardiac Morphology - Summer Edition
London, United Kingdom

August 27-31
ESC 2011 - European Society of Cardiology Congress 2011
Paris, France

October 23-26
9th International Congress on Coronary Artery Disease
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Instructions to authors

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The columns in the issues of *WJC* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Articles: To report innovative and original findings in cardiology; (9) Brief Articles: To briefly report the novel and innovative findings in cardiology; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJC*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of cardiology; and (13) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on the research in cardiology.

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stepwise), correlation, analysis of variance, analysis of covariance, *etc*. The reviewing points include: (1) Statistical methods should be described when they are used to verify the results; (2) Whether the statistical techniques are suitable or correct; (3) Only homogeneous data can be averaged. Standard deviations are preferred to standard errors. Give the number of observations and subjects (*n*). Losses in observations, such as drop-outs from the study should be reported; (4) Values such as ED50, LD50, IC50 should have their 95% confidence limits calculated and compared by weighted probit analysis (Bliss and Finney); and (5) The word 'significantly' should be replaced by its synonyms (if it indicates extent) or the *P* value (if it indicates statistical significance).

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Organization as author

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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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Books

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Conference paper

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Electronic journal (list all authors)

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

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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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