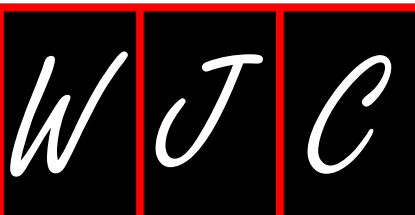


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diet, smoking, and sleep, play a major role in preventing the development and progression of cardiovascular disease (CVD). Among these behaviors, sleep may play a pivotal role, yet it has been studied somewhat less than other behaviors and there have been few well-designed sleep intervention studies targeting CVD. Furthermore, despite the fact that these behaviors are often inter-related, interventions tend to focus on changing one health behavior rather than concurrently intervening on multiple behaviors. Psychological constructs from depression to positive affect may also have a major effect on these health behaviors and ultimately on CVD. In this review, we summarize the existing literature on the impact of sleep and other cardiac health behaviors on CVD onset and prognosis. We also describe interventions that may promote these behaviors, from established interventions such as motivational interviewing and cognitive behavioral therapy, to more novel approaches focused on mindfulness and other positive psychological constructs. Finally, we outline population-health-level care management approaches for patients with psychiatric conditions (*e.g.*, depression) that may impact cardiac health, and discuss their potential utility in improving mental health, promoting health behaviors, and reducing CVD-related risk. Much work is still needed to better understand how sleep and other health behaviors may uniquely contribute to CVD risk, and additional high-quality studies of interventions designed to modify cardiac health behaviors are required to improve cardiovascular health in individuals and the population at large.

Key words: Sleep; Diet; Physical activity; Cardiovascular disease; Care management

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Abstract

Numerous health behaviors, including physical activity,

Core tip: This manuscript discusses the link between modifiable health behaviors; including sleep, diet, activity, and their relationship to adult risk for cardiovascular disease. Despite knowing that these behaviors are

often interrelated, interventions to date have primarily focused on changing one health behavior *vs* intervening on multiple behaviors simultaneously. Population health level care management approaches are outlined to aide providers in counseling their patients.

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INTRODUCTION

Recent guidelines for adequate sleep duration from the American Academy of Sleep Medicine and Sleep Research Society state that a typical adult needs at least 7 h of sleep each night to maintain optimal health^[1,2]. Population-based studies estimate that one in three adults in the United States report sleeping fewer than 7 h per night^[3,4]. This statistic is alarming as research has shown that individuals with insufficient sleep are at a significantly greater risk for many chronic diseases, including cardiovascular disease (CVD)^[5-8], which is responsible for one in four deaths in the United States^[9]. Additional health behaviors beyond sleep, including poor diet, low levels of physical activity, and prolonged sedentary time, are also major risk factors for the development of CVD^[6]. This review will discuss the current literature linking these modifiable health behaviors to an increased risk of CVD, and the evidence-based interventions that can modify them, in order to guide future intervention targets and strategies aimed at reducing CVD risk in adults.

IMPORTANCE OF SLEEP IN REDUCING CVD RISK

In recent literature, both insufficient sleep duration (most often defined as fewer than 7 h) and long sleep duration (more than 9 h) have been associated with poor health outcomes and increased mortality risk^[6,10]. In one such large, population-based study, individuals who reported fewer than 6 h of sleep had a 15% higher incidence of CVD compared to those who reported sleeping between 7-8 h^[8].

Many biomarkers related to CVD risk have been examined in relation to insufficient sleep duration. The relationship between short sleep duration and hypertension is well documented, extending from experimental studies to longitudinal epidemiological studies and intervention studies^[11-13]. Short sleep duration (collected *via* self-report questionnaire) has been associated with higher blood pressure in cross-sectional studies and greater overall incidence of hypertension in population studies. Studies tend to vary in their definition

of short sleep duration, but overall conclude that 5 or fewer hours of sleep each night is related to the worst blood pressure outcomes. These poor blood pressure outcomes are reported to be most common in women and adults who are less than 65 years old. Racial/ethnic differences have been found showing that relationships between short sleep duration (fewer than six hours per night) and hypertension are strongest in non-Hispanic whites, blacks, and Hispanics/Latinos populations^[5].

Insufficient sleep has also been associated with other conditions linked with CVD, such as obesity and type 2 diabetes mellitus (T2DM). Short sleep duration has been strongly linked to an increased risk of obesity across all populations^[14], and, conversely, for each additional hour of sleep an individual's body mass index (BMI) decreases by 0.35 units^[14]. Racial/ethnic differences have been found, with the strongest relationship of very short sleep (less than five hours per night) and obesity in individuals who identify as African American/black^[5]. Further research has shown that women who reported sleeping less than 6 h per night over the course of 16 years gained significantly more weight compared to women that slept at least 7 h^[15]. Individuals with short sleep duration (fewer than 6 h per night) have also been shown to have an increased risk of T2DM^[16,17]. It remains unclear whether this increased risk is mediated by obesity or if there are other mechanisms, including glucose metabolism, that may explain the increased risk of T2DM.

There is less data on the connection between short sleep duration and other biological markers of health^[6]. Regarding inflammatory markers, when sleep is experimentally restricted to fewer than four hours per night, increases in C-reactive protein and interleukin-1 receptor have resulted^[18,19]. Studies examining the effects of short sleep duration and insulin resistance are also rare. Self-report of fewer than 6 h of sleep per night has been associated with increased insulin and hemoglobin A1C (HbA1c), but this result was attenuated when BMI was added to the model^[20]. Studies of sleep restriction (fewer than 6 h in bed) have found an increase in insulin resistance^[21,22]; however, these studies were limited to healthy, young males. Therefore, the relevance of these associations to the general population remain unclear.

Importance of other health behaviors in reducing CVD risk

Dietary intake, physical activity, and sedentary time have also been associated with CVD risk in adults. The effects of numerous dietary components on CVD risk have been examined^[23]. For example, adherence to a Mediterranean diet, consisting of a high intake of fruits and vegetables, fish, olive oils, and dairy, has been associated with a lower risk of CVD events including myocardial infarction and stroke as well as lower cardiovascular mortality^[24]. A similar dietary eating pattern, the DASH eating plan, consisting of fruits and vegetables, low-fat dairy, whole grains, poultry, fish, and nuts, has also been found to lower incidence of adverse cardiovascular events^[25]. Specific dietary components have also been associated

with a reduced risk of CVD. Diets high in polyunsaturated fatty acids and low in sodium have are linked to fewer cardiovascular events^[23]. Increasing physical activity levels, at any intensity level, has been shown to lower CVD risk. Individuals with higher daily overall physical activity (measured *via* accelerometer) and moderate-vigorous physical activity have been shown to have lower CVD mortality^[26]. Although reducing sedentary time appears important to overall health, sedentary time has generally not been associated with CVD mortality^[26].

POTENTIAL RELATIONSHIPS BETWEEN MULTIPLE HEALTH BEHAVIORS IN REDUCING CVD RISK

Despite the strong evidence of increased CVD risk associated with each of the above behaviors on poor health outcomes, an important issue in this line of research is detangling the effects of these health behaviors from one another, as they tend to be strongly correlated within individuals. Due to this, it can be difficult to discern which health behaviors independently contribute to improved health outcomes. For example, there is limited data regarding how sleep combines with the other behaviors. Additional evidence is needed to define how these behaviors may cluster or pattern together resulting in an increased risk of disease; such knowledge can help to inform future public health intervention guidelines and policy in this area. Intervention and policy strategies to date have focused on changing individual behaviors, with very few strategies attempting to target multiple lifestyle behaviors simultaneously^[27]. A study in over 500000 United Kingdom adults aged 37-63 years found that individuals with CVD were more likely to report low levels of physical activity, more than 3 h of TV viewing per day, and fewer than 7 h of sleep per night, compared to individuals without CVD^[27]. The clustering of these behaviors was termed a “unhealthy phenotype” and individuals with this unhealthy phenotype had poorer disease outcomes.

Multiple health behavior interventions have been shown to have improved health outcomes, such as blood pressure, cholesterol, and glucose, when changes to both diet and activity are changed simultaneously^[28]. However, there is very limited evidence to date that these types of interventions directly impact CVD events or mortality^[28].

STANDARD HEALTH BEHAVIOR INTERVENTIONS AND THEIR IMPACT IN CVD RISK POPULATIONS

Cognitive-behavioral therapy

Cognitive-behavioral therapy (CBT) is an evidence-based intervention for improving cardiac health behaviors and outcomes. It is a short-term skills-based psychotherapy that teaches cognitive (*e.g.*, cognitive restructuring,

probability estimation) and behavioral strategies (*e.g.*, behavioral exposures, behavioral activation) to reduce emotional distress, improve well-being, and promote healthy behavioral choices. Originally developed for treating emotional problems, CBT is often most useful for improving health behaviors among patients with or at risk for chronic medical conditions who may be more motivated for change, and psychiatric symptoms among individuals with mental health disorders who have the greatest room for symptom improvement. For example, in a study of CBT for improving sleep in healthy college students, only those with poor sleep at baseline showed significant improvement (Trockel *et al.*, 2011). Thus, much of the work on CBT and cardiac risk factors has been aimed at improving sleep and other health behaviors and psychiatric symptoms in patients with insomnia, mental health problems, or those with or at risk for CVD. Table 1 shows representative studies examining the effects of standard health behavior interventions on health outcomes.

CBT is useful for improving sleep and other health behaviors in patients with or at risk for CVD. A recent review of CBT for insomnia (CBT-I) in CVD patients found that there is limited but promising evidence for CBT-I to improve sleep characteristics (*e.g.*, sleep efficiency and quality), CVD biomarkers, symptom burden, functional impairment, and quality of life^[29,30]. CBT has also been shown to improve health behaviors including diet (*e.g.*, reduced sugar, increased fruits/vegetables), physical activity, and smoking cessation in some studies of healthy adults and those with or at risk for CVD^[31-35].

In line with the original aim of CBT, much of the research on CBT and cardiac health has focused on the efficacy of CBT in improving psychosocial problems in CVD patients given that these problems have a significant negative impact on cardiac morbidity and mortality^[36,37]. The results of several randomized clinical trials (RCT) support the efficacy of CBT in improving depression, anxiety, and quality of life in CVD patients, patients suffering an acute coronary syndrome (ACS), heart surgery patients, and heart failure patients^[38-44]. A systematic review and meta-analysis of psychological interventions for depression in CVD found that CBT had the strongest effects^[45], and the American Heart Association specifically recommends CBT for treating depression in CVD patients^[46]. CBT is also associated with improved psychosocial outcomes among individuals at risk for CVD including those with type 2 diabetes, hypertension, and overweight and obesity^[31,34,47].

Evidence for direct effects of CBT on physical health outcomes is less consistent. A Cochrane review of 64 RCTs found that psychological interventions produced small-moderate improvements in depression and anxiety and a small effect on cardiac mortality in CVD patients, but no effect on total death or cardiac events^[44]. Another systematic review found improvements in depression symptoms but no effect on all-cause mortality, cardiac mortality, or cardiac events^[43]. In the Enhancing Recovery in Coronary Heart Disease Patients trial, a randomized trial of 2481 post-ACS patients, CBT was asso-

Table 1 Representative studies examining the effects of cognitive behavioral therapy and motivational interviewing on health-related outcomes

Ref.	Population	Intervention	Outcome
Tsiros <i>et al</i> ^[33] , 2008	<i>n</i> = 47 adolescents with overweight or obesity	CBT <i>vs</i> no-treatment	Greater improvements in weight, BMI, body fat, sugar intake (soft drinks) in CBT group at 20-wk follow-up
Welschen <i>et al</i> ^[34] , 2013	<i>n</i> = 154 diabetes patients	CBT <i>vs</i> managed care	Greater improvement in physical activity, quality of life, and depression in CBT group at 6-mo follow-up; no group differences at 12-mo follow-up
Freedland <i>et al</i> ^[39] , 2009	<i>n</i> = 123 CABG patients with depression	CBT <i>vs</i> supportive stress management	Greater depression remission in CBT than supportive stress management group at 3-mo and 9-mo follow-up
Berkman <i>et al</i> ^[48] , 2003	<i>n</i> = 2481 MI patients	CBT <i>vs</i> usual care	Greater improvement in depression and social support in CBT group at 6-mo follow-up; no group differences in survival at 29-mo follow-up
Woollard <i>et al</i> ^[55] , 1995	<i>n</i> = 166 patients with hypertension	MI low dose <i>vs</i> MI high dose <i>vs</i> usual care	Greater improvements in alcohol and salt intake in low-MI <i>vs</i> usual care; greater improvements in weight and blood pressure in high-MI <i>vs</i> usual care at 18-wk follow-up
Ma <i>et al</i> ^[59] , 2014	<i>n</i> = 120 Chinese patients with hypertension	MI <i>vs</i> usual care	Greater improvements in treatment adherence and blood pressure in MI group
Ogedegbe <i>et al</i> ^[60] , 2008	<i>n</i> = 190 African American patients with hypertension	MI <i>vs</i> usual care	Greater improvements in medication adherence and blood pressure in the MI group at 12-mo follow-up
Cain <i>et al</i> ^[68] , 2011	<i>n</i> = 104 adolescents	MI and sleep education <i>vs</i> no intervention	Greater improvements in sleep knowledge and out-of-bed time in MI group; improvements in sleep and daytime functioning in both groups

BMI: Body mass index; CABG: Coronary artery bypass graft; CBT: Cognitive behavioral therapy; MI: Motivational interviewing.

ciated with improvements in depression symptoms, but did not affect survival or cardiac events at 6-mo follow-up^[48]. It is possible that longer-term follow-up is needed to identify physical health benefits of CBT, which may take time to develop and require continued use of CBT skills^[49,50].

Recent studies have explored telephone-based and web-based CBT interventions for improving psychosocial outcomes in patients with CVD. These studies have shown mixed but promising results. For example, a RCT of telephone-delivered CBT for post-ACS patients with depression found greater improvements in depression symptoms following CBT as compared to usual care, with effects maintained up to one year later^[42]. A pilot study of web-based CBT for heart failure patients also found improvements in depression symptoms though there were no significant between-group differences^[51]. In a study of post-transplant patients, however, telephone-delivered CBT was not found to be acceptable, and while patients who did participate showed significant reductions in anxiety and depression symptoms, most (67%) continued to show elevated scores^[52]. Given that there is evidence of potential feasibility and efficacy, and mobile health interventions have the potential to improve access to mental health care for CVD patients^[53], further controlled studies should explore virtual CBT interventions

be delivered remotely by different avenues with good fidelity^[56,57]. MI interventions have led to improved health behaviors in patients with cardiac risk factors, including increased physical activity in patients with diabetes^[58] and hypertension^[59]. Additional studies have demonstrated improved medication adherence and significant reductions in systolic blood pressure in patients with hypertension^[60-62]. Furthermore, a Cochrane review of MI for smoking cessation showed a modest but significant increase in quitting compared to usual care^[63]. There are several ongoing trials assessing the potential of different MI-based interventions to improve other health behaviors and cardiac risk factors, including improving statin adherence in patients with hypercholesterolemia^[64], optimizing risk factors in patients undergoing cardiovascular procedures^[65], and comparing group-based to individual MI interventions in patients at high risk for CVD^[66]. Although few interventions have used MI to modify sleep behaviors^[67,68], MI may be well-suited to address sleep in a manner similar to that used for other health behaviors. Further, despite MIs extensive use in research studies and clinical care, the effects of solely MI-based interventions for activity promotion in patients with T2D^[58] and other major cardiac risk factors may not be significant enough to prevent CVD or major cardiac events, raising the possibility that additional interventions may be necessary in these patients.

MI based interventions and their impact in CVD risk population

An even more traditional approach to health behavior change is motivational interviewing (MI). Over 30 years of research have established MI, a patient-centered method for identifying and enhancing intrinsic motivation, as an effective and straightforward technique for promoting behavioral change^[54,55]. MI is effective and can

NOVEL INTERVENTIONS TO TARGET HEALTH BEHAVIORS AND CARDIAC OUTCOMES

Mindfulness and mind-body interventions

Mindfulness and other mind-body interventions have

received increased attention for improving cardiac health behaviors and outcomes. Mind-body interventions encompass a range of techniques that aim to unite the body and mind to promote well-being, such as progressive muscle relaxation, meditation, yoga, and tai chi. Mindfulness is a specific approach that involves paying attention to present moment experiences with an attitude of openness, non-judgment, and curiosity^[69]. A large body of research supports the efficacy of mind-body interventions, particularly mindfulness-based interventions that incorporate elements of CBT (e.g., mindfulness-based stress reduction, mindfulness-based cognitive therapy) for improving a range of physical and mental health outcomes (e.g., Hofmann *et al.*^[70], 2010).

Mindfulness-based interventions may improve cardiac health behaviors. Recent systematic reviews have concluded that mindfulness interventions promote smoking cessation^[71] and healthy eating^[72]. Evidence for improvements in sleep are somewhat limited, with a systematic review finding few randomized controlled trials and no significant between-group differences in sleep outcomes, but a significant correlation between amount of mindfulness meditation practice and improved sleep^[73]. Subsequent RCTs, however, have found significant effects of mindfulness training on insomnia^[74]. There has been less research using mindfulness-based interventions to promote physical activity, though there is some evidence to suggest that mindfulness training can increase physical activity in healthy young adults^[75] and CVD patients^[76], and that the ability to be mindful during daily life in general (i.e., trait mindfulness) might increase physical activity levels by making activity seem more satisfying^[77].

Mindfulness-based interventions have also been associated with improved health outcomes in patients with and at risk for CVD. Research suggests that mindfulness training can promote weight loss among patients with obesity^[78]; improve disease management and HbA1c levels among patients with diabetes^[79]; and improve coping and blood pressure in patients with hypertension^[80]. A systematic review among individuals with CVD or other risk factors (e.g., hypertension and diabetes patients) found significant improvements in stress, depression, anxiety, and quality of life following mindfulness interventions; however, similar to studies of CBT, effects on physical health outcomes were less consistent^[49]. Among CVD patients specifically, a systematic review of 11 RCTs of mind-body practices found significant improvements in depression, anxiety, and QoL, though these studies were found to be of overall low quality^[81]. Mindfulness-based interventions have also been integrated into cardiac rehabilitation programs^[82], and several studies suggest that meditation, tai chi, and yoga may be useful for improving health outcomes in heart failure patients^[83-85]. Indeed, a systematic review of 29 trials (9 RCTs) found that tai chi is associated with reduced blood pressure and exercise capacity in patients with CVD and risk factors^[86]. Further research on mind-body interventions for CVD risk

behaviors and outcomes is needed, though providers should be aware that existing mind-body approaches may be useful for cardiovascular outcomes.

Positive psychological interventions for health behavior and cardiac outcome improvement

There has been increasing interest in the use of positive psychology (PP) interventions that aim to boost positive emotional experiences and cognitive processes through the use of simple tasks focusing on positive psychological constructs, such as optimism and positive affect. These positive constructs have been shown to correlate with improved adherence to cardiac health behaviors, such as physical activity^[87,88], diet^[89,90], and medication adherence^[91]. They have further been associated with improved rates of heart disease and cardiac mortality^[92-94]. Specific PP exercises found effective in medically healthy persons include recalling and discussing positive events, identifying and deliberately using personal strengths, and planning and performing acts of kindness^[95,96].

PP interventions are simple for patients and do not require extensive provider training, raising the attractive possibility of a cost-effective and efficient means of improving mood and cardiac health behaviors. Despite this, there has been limited study of PP-based interventions to promote health behaviors, improve sleep, or reduce cardiac events or mortality. PP interventions have been applied in studies of T2D^[97] and immunodeficiency virus^[98], and a meta analysis has shown that their successful implementation leads to improvements in psychological outcomes^[99]. Positive psychology interventions focused on gratitude have also promoted improvement in sleep hours and quality in patients with neuromuscular disease^[100].

Among patients with existing CVD, there is a small literature on PP interventions^[101-103], generally finding that such interventions are well-accepted and have beneficial effects on both positive and negative psychological states^[101-106]. Additionally, randomized controlled trials of positive affect interventions have shown increased medication adherence in hypertensive patients^[104] and improved physical activity in patients post-percutaneous coronary intervention^[105]. Furthermore, combining PP with established health behavior interventions could provide additional benefit, building on the literature showing that PP exercises lead to increases in self-efficacy, confidence, and interpersonal connectedness^[106-108] and findings that these same characteristics can improve engagement in health behavior interventions^[109,110].

Management of mental health conditions/care management

Additional novel approaches to modifying health behaviors *via* mental health-related interventions may include care management programs for patients with psychiatric conditions. Depression and other psychiatric syndromes are common in patients with, or at risk for,

CVD^[111,112], and they can be identified *via* systematic screening in clinical cardiology settings^[113]. Patients with depression and related conditions are at substantially elevated risk for nonadherence, including nonadherence to cardiac health behaviors^[114-116]. Given the high prevalence and substantial impact of these psychiatric conditions, utilizing population-based interventions to efficiently manage these conditions is a promising approach to improving psychiatric symptoms, health behavior adherence, and overall cardiac risk in the greatest number of patients. For example, “collaborative care” interventions utilize a non-physician care manager (often a nurse) to assess and longitudinally monitor psychiatric conditions for patients in inpatient and outpatient medical settings^[117,118]. The care manager can also provide psychotherapeutic interventions and support to patients, and receives psychiatric medication recommendations when indicated from a team psychiatrist. These medication recommendations are conveyed to primary care physicians, who then prescribe all medications. This allows a large number of patients to receive ongoing and expert management of psychiatric care, while maintaining such care within their existing medical home.

Collaborative care interventions have been found to be effective in improving psychiatric symptoms in over 90 prior trials^[117]. This includes several prior trials in patients with CVD or cardiac risk factors (e.g., diabetes)^[118-124], with beneficial effects on depression and/or anxiety symptoms. They have not typically included specific interventions to improve sleep or other health behaviors, and they have had more mixed effects on adherence, with some trials finding improvement in adherence to health behaviors (e.g., diet, exercise, and medication adherence)^[120,125], while others have not measured effects on adherence or found no significant change. Effects on cardiovascular outcomes have similarly been mixed, though an analysis of the large IMPACT trial of collaborative care found that the intervention was associated with lower risk of cardiovascular events among those participants with no CVD at the outset of the trial^[126].

One promising approach to improving behavioral and cardiovascular outcomes is a “blended” collaborative care management approach that utilizes a nurse care manager to address depression, health behaviors, and medical targets (e.g., blood pressure) in patients with medical illness. The TEAMCare randomized trial tested such an approach in patients with diabetes or coronary artery disease, and found that such an intervention led to improved medical outcomes, including hemoglobin A1c and blood pressure, using this combined psychiatric, behavioral, and medical approach^[127]. The COMPASS project then implemented this intervention in 172 real-world clinics among 3609 patients^[128,129]. Overall 40% had depression remission or response, one-quarter met criteria for control of blood glucose, and nearly 60% met criteria for blood pressure control, impressive findings for real-world implementation in a

complex population.

CONCLUSION

The importance of sleep as a health behavior to lower the risk of CVD in adults has not been widely studied. With recent guidelines shedding light on the importance of adults maintaining adequate sleep (defined as at least seven hours) for optimal health and the growing number of Americans not meeting this recommendation, future research needs to include sleep when assessing CVD risk factors and intervention targets. Research to date has primarily focused on other health behaviors including diet, physical activity, and sedentary time. Many of these interventions have focused on one health behavior, rather than changing multiple behaviors, despite the fact that these behaviors tend to be inter-related. The same theories and intervention strategies used to change individual health behaviors, including CBT, MI, mindfulness and mind-body interventions, and PP-based interventions, could be adapted to promote all relevant health behaviors as we have outlined in this review. Further, moving toward blended collaborative care models may be a promising approach to improve health behaviors in those with psychiatric conditions. Such interventions that focus on psychological status, health behaviors, and medical targets may indeed hold substantial promise to modify sleep and other health behaviors to reduce cardiac risk.

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Heart failure after myocardial infarction in the era of primary percutaneous coronary intervention: Mechanisms, incidence and identification of patients at risk

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Abstract

Myocardial infarction (MI) remains the most common cause of heart failure (HF) worldwide. For almost 50 years HF has been recognised as a determinant of

adverse prognosis after MI, but efforts to promote myocardial repair have failed to translate into clinical therapies. Primary percutaneous coronary intervention (PPCI) has driven improved early survival after MI, but its impact on the incidence of downstream HF is debated. The effects of PPCI are confounded by the changing epidemiology of MI and HF, with an ageing patient demographic, an increasing proportion of non-ST-elevation myocardial infarction, and the recognition of HF with preserved ejection fraction. Herein we review the mechanisms of HF after MI and discuss contemporary data on its incidence and outcomes. We review current and emerging strategies for early detection of patients at risk of HF after MI, with a view to identification of patient cohorts for novel therapeutic agents.

Key words: Angioplasty; Heart failure; Myocardial infarction; Percutaneous coronary intervention; ST-elevation myocardial infarction

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Core tip: Heart failure (HF) is a major cause of late morbidity and mortality after myocardial infarction. Several approaches exist for early identification of patients at risk of HF, including clinical and angiographic scoring, cardiac imaging, and invasive coronary physiology, but these are currently poorly integrated. Here we provide an overview of the incidence, mechanisms, and outcomes of HF following myocardial infarction in the era of primary percutaneous coronary intervention, and discuss HF risk-stratification for the individual patient. Looking ahead, accurate and early prediction of HF will allow targeting of novel therapeutic agents to high-risk patients before ventricular remodelling and clinical HF have become established.

Cahill TJ, Kharbanda RK. Heart failure after myocardial infarction

in the era of primary percutaneous coronary intervention: Mechanisms, incidence and identification of patients at risk. *World J Cardiol* 2017; 9(5): 407-415 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i5/407.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i5.407>

INTRODUCTION

Primary percutaneous coronary intervention (PPCI) has revolutionised the management and outcome of acute myocardial infarction (MI)^[1,2]. It is the reperfusion strategy of choice throughout the developed world, with 90000 procedures performed annually in the United States alone^[3,4]. Contemporary PPCI in the United Kingdom is characterised by door-to-balloon times of < 60 min, radial access, second generation drug-eluting stents and tailored use of antiplatelet and antithrombotic agents^[5,6]. The introduction of PPCI and adjunctive therapies have driven a reduction in inpatient mortality following acute MI from 20% in the late 1980s to approximately 5%-7% in contemporary series^[7,8].

Despite this success, coronary artery disease remains the commonest cause of heart failure (HF)^[9]. HF after MI is the major driver of late morbidity, mortality and healthcare cost. The effect of PPCI on the incidence of HF is debated, with studies confounded by the changing definitions and epidemiology of both MI and HF. Targeted therapies to prevent HF after MI have lagged behind advances in reperfusion, with Entresto (valsartan/sacubitril) the only novel pharmacotherapy for HF to enter the mainstream market in over a decade. Despite the evident burden of HF, many MI trials have predominantly focused on thrombosis, bleeding and composite endpoints [e.g., major adverse cardiac events (MACE)] rather than HF events specifically.

In this review we outline the challenge of HF following MI in contemporary practice. We provide an overview of the mechanisms and definitions of HF after MI, and the data on temporal trends in HF incidence from the pre-thrombolysis era through to the modern day. We review current and emerging strategies to identify patients at risk of HF, including coronary physiology, cardiac magnetic resonance and hybrid imaging, and suggest how improved mechanistic understanding of HF can be used to inform the next generation of clinical trials for these patients.

DEFINING HF AFTER MI

HF is defined as "a clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill or eject blood"^[10]. This has been translated into several validated diagnostic criteria (e.g., the Framingham criteria^[11] and the European Society of Cardiology criteria^[12]), but the primary definition of HF as a clinical syndrome has led to differing clinical, imaging and biomarker definitions

coexisting in clinical practice and research. Unlike MI, there is no "universal definition" and consequently, the diagnosis of HF is often heterogeneous between studies and over time^[13].

Early studies of HF following MI used clinical criteria such as the Killip and New York Heart Association classifications^[14,15]. While crude, Killip class has retained prognostic value in more recent cohorts such as the GRACE registry: Patients in Killip class I had an in-hospital mortality of 3%, rising to 20% for those in class III^[16]. In the PPCI population, higher Killip class at presentation is an independent predictor of in-hospital and 6-mo mortality^[17]. Clinical HF scores were refined by the development of echocardiography, which led to objective measurement of ejection fraction and ventricular volumes as an intrinsic part of a HF diagnosis^[18].

The timing of HF following MI is important clinically, mechanistically and for research. Three key time periods need to be distinguished: HF at the index MI presentation, during the course of the first admission, and after discharge. The timing of HF is often not well-defined by research studies, making comparison between studies challenging. From a statistical perspective, older studies failed to treat HF as a time-dependent, evolving covariate whose incidence was modifiable by the up-front treatment, meaning that late-onset HF after MI is less well characterised than HF at presentation^[19].

PATHOPHYSIOLOGY OF HF AFTER MI

Several overlapping mechanisms contribute to HF after MI (Figure 1). HF during the index MI occurs due to a combination of myocardial stunning, myocyte necrosis, decompensation of pre-existing HF or acute mitral regurgitation due to papillary muscle dysfunction. HF during the hospitalisation may also be due to any of the above, compounded by fluid or contrast overload, renal dysfunction, or complications such as ventricular septal defect or cardiac tamponade. Late HF reflects the consequences of cardiomyocyte death and scar formation occurring alongside ventricular remodelling.

The cellular pathophysiology of MI has been clearly defined in animal models. Within 30 min of ischaemia, cardiomyocyte structural changes and oedema develop, leading to progressive cell death from three hours. Acute contractile dysfunction occurs due to oxidative stress and calcium overload, which is reversible if flow is restored^[20]. Reperfusion itself causes a second wave of injury, by production of reactive oxygen species. Despite successful epicardial reperfusion, embolization of thrombotic debris, plugging by inflammatory cells and release of vasoactive mediators from damaged endothelium leads to ongoing microvascular dysfunction in up to 50% of patients^[21].

Myocardial injury leads to activation of a stereotyped inflammatory cascade, comprised of early neutrophil ingress followed by monocyte-macrophage infiltration.

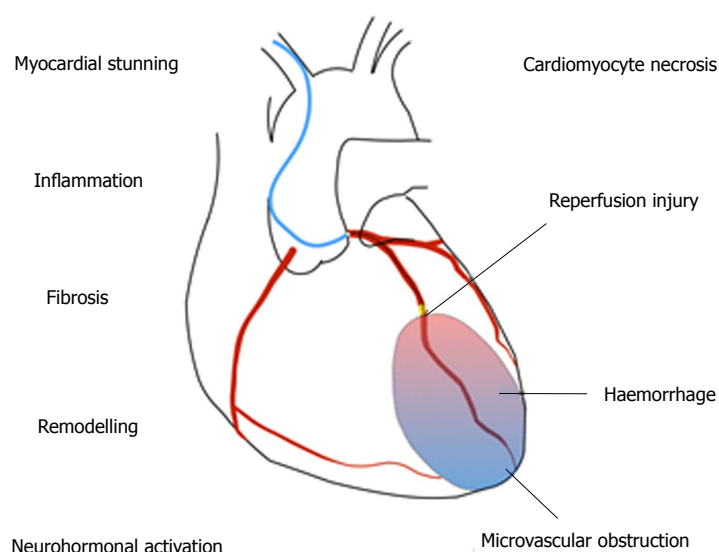


Figure 1 Mechanisms of heart failure after myocardial infarction.

Between days 3-5 following MI there is a transition from inflammation to repair, with activation of fibroblasts and progressive scar deposition^[22]. Over time there is compensatory activation of the renin-angiotensin and sympathetic nervous systems and pathological remodelling, with changes to the ventricular geometry, wall thinning, ischaemic mitral regurgitation and further cardiomyocyte loss. The precise contribution of the different pathophysiological components (*e.g.*, microvascular dysfunction, inflammation) to injury is likely to be heterogeneous, and understanding mechanistic pathways in specific patient subgroups will be key to identifying novel therapeutic strategies^[23].

TEMPORAL TRENDS IN HF AFTER MI

HF after MI was first described as an adverse prognostic feature by Killip in the 1960s^[14]. HF was associated with large infarcts and multivessel disease, and the presence of impaired ventricular function was linked to worsening mortality^[24,25]. Prior to thrombolysis, the incidence of in-hospital HF after ST-elevation myocardial infarction (STEMI) was approximately 40%^[15]. This appeared to reduce after the introduction of thrombolysis, with HF present in approximately 3% of patients at presentation and 17% during admission^[26]. Successful reperfusion was associated with improved LV function and long-term survival^[27]. HF during admission remained an adverse prognostic feature, with 1-year mortality rates approximately 5 fold higher in those with HF^[28].

More recent studies have suggested a further reduction in HF rates with use of primary PCI. In an Italian cohort of 2089 MI patients treated exclusively by PPCI between 1995 and 2005, 17% presented in HF, but only a further 1% developed new onset HF during the hospital admission^[29]. Similarly, in an analysis from the HORIZONS-AMI cohort of 3602 patients recruited between 2005-2007 treated with PPCI, 8.0% of patients

were in Killip class II-IV at presentation. At 30 d, only 4.6% of patients had developed a clinical HF syndrome (defined by NYHA/Killip class), rising to 5.1% at 2 years^[30].

These studies are not directly comparable, and reflect selected trial cohorts with a short duration of follow-up and differing methods of HF ascertainment. Several dedicated time trend analyses have now been performed. In Olmsted County, 1537 patients with an index MI between 1979 and 1994 were identified, spanning the introduction of thrombolysis in the late 1980s^[31]. Over the study period the 5-year incidence of HF decreased from 40% to 33%. In a later study of 2596 MI patients between 1990 and 2010, there was increasing use of PPCI and a reduced risk of both early (0-7 d; HR = 0.67, 95%CI: 0.54-0.85) and late (8 d-5 years; HR = 0.63, 95%CI: 0.45-0.88) HF over time^[32]. In patients with HF, mortality was higher for those with delayed vs early onset HF^[33].

A reduction in post-MI HF has also been seen in other studies. In a sample of 2.8 million MI hospitalisations (in Medicare beneficiaries) between 1998-2010, there was a reduction in the incidence of subsequent HF hospitalisation from 16 to 14 per 100 person-years^[34]. In a Danish cohort, the incidence of HF at 90 d post-MI reduced from 24% to 20% alongside a an increase in PCI from 2.5% to 38% between 1997 and 2010^[35]. Similarly, in Western Australia there was a reduction in the prevalence of HF at 90 d from 28% to 17% between 1996 and 2007^[36]. Finally, in the SWEDEHEART registry of 199851 patients admitted with an MI between 1996 and 2008, there was a reduction in the incidence of clinical HF (albeit measured during the index hospitalization) from 46% to 28% alongside increasing use of PPCI^[37].

In contrast, data from Framingham Heart Study shows an increase in HF over time^[38,39]. In 676 patients who developed a first MI between 1970 and 1999, both the 30-d and 5-year incidence of HF increased. At

Infarct size/characterisation		Salvage/repair
Age	Patient	Age
Male sex		Killip class
Killip class		Pain to balloon time
Pain to balloon time		
LAD culprit artery	Angiography	Pre-PCI TIMI flow
TIMI flow pre/post PCI		Collateral flow
MBG		
IMR	Coronary physiology	IMR
CFR		Δ CFR
Cardiac function/volumes	Echocardiography	
WMSI		MVO
MVO	Cardiac MRI	Δ Cardiac function
Infarct haemorrhage		Δ Cardiac volumes
Cardiac function/volumes		- remodelling
Inflammation	PET	Required
CK/TnI and BNP	Biomarkers	Required

Figure 2 Heart failure after myocardial infarction - strategies for prediction of infarct size and salvage. BNP: B-type natriuretic peptide; CFR: Coronary flow reserve; CK: Creatine kinase; IMR: Index of microcirculatory resistance; LAD: Left anterior descending; MBG: Myocardial blush grade; MVO: Microvascular occlusion; PET: Positron emission tomography; PCI: Percutaneous coronary intervention; TIMI flow: Thrombolysis In Myocardial Infarction flow score; TnI: Troponin I; WMSI: Wall motion score index.

5 years, the incidence of HF was 28% in 1970-1979 and 32% in 1990-1999, which remained significant after multivariate adjustment, with a risk ratio of 1.74 (95%CI: 1.07-2.84) for HF in 1990-1999 compared with 1970-1979^[39]. Similarly, the Worcester Heart Attack Study showed an increasing incidence of HF between 1975 and 2001, and in the Alberta Elderly MI cohort, there was a 25% increase in the incidence of in-hospital HF between 1994-2000, from 31% to 39%^[40,41].

In the face of conflicting data from a relatively small number of studies, it remains difficult to draw firm conclusions on the impact of PPCI on the incidence of HF. There are key differences between studies in the definition of HF and MI, the validation of these diagnoses, the timing of ascertainment and the duration of follow-up. While the majority appear to suggest that PPCI is associated with reduced HF incidence, for many the duration of follow-up is short. Some studies have not differentiated between incident and prevalent cases. Reconciling these differences will require further studies with long term follow-up. If increasing survival from MI is leading to a rise in HF, this may only be seen in updated analyses, as interventionalists take on increasingly frail and elderly patients who previously were not surviving^[42].

RISK STRATIFICATION FOR HF AFTER MI

Given the ongoing contribution of HF to morbidity and mortality after MI, early risk stratification and preventative therapeutic strategies are required. Although a number of clinical, angiographic, physiological, imaging and biomarker approaches to HF risk stratification following MI have been proposed (Figure 2), few are in routine clinical use. In addition to prognostication,

emerging hybrid imaging and coronary physiology approaches are shedding light on the mechanisms driving HF in different patient subgroups, and might also be used as early surrogate endpoints for trials. Given the historical failure of generic approaches targeting processes such as inflammation, it seems likely that tailored therapies for specific patient groups will be required.

Clinical evaluation

Infarct size is the major determinant of downstream HF and prognosis^[43]. Predictors of HF on admission are related to underlying LV function (e.g., prior MI), markers of coronary artery disease severity (e.g., diabetes mellitus) and features of an extensive infarct (e.g., anterior location, increasing duration from symptom onset to reperfusion)^[29]. Clinical predictors of late HF are of greater use for risk stratification. In the HORIZONS-AMI cohort, predictors of new-onset HF at 2 years were a history of MI (OR = 1.81, 95%CI: 1.22-2.67), ejection fraction (per 10% decrease OR = 1.35, 95%CI: 1.21-1.5), female sex (OR = 1.34, 95%CI: 1.1-1.51) and insulin-treated diabetes (OR = 1.68, 95%CI: 0.96-2.65)^[30]. Similarly, in the CARE and VALIANT studies of MI survivors, predictors of late HF were age, diabetes, renal insufficiency, LVEF post-MI, and Killip class at index MI ≥ 2 ^[44,45]. A dedicated scoring system for prediction of late HF which integrated these parameters would be of value. Although not designed for HF events, the GRACE score, originally developed for ACS risk stratification, has recently been shown to predict late HF events after both STEMI and NSTEMI^[46].

Coronary angiography and haemodynamics

Coronary angiography provides a number of patient-

specific markers for risk stratification, albeit often for MACE rather than HF specifically (Figure 2). The presence of multivessel disease and lack of normal flow in the infarct related artery are key adverse prognostic features after PPCI^[47,48]. TIMI flow in the infarct related artery pre and post-procedure predicts outcome, with post-procedural \leq TIMI 2 flow associated with a HR of 3.8 (95%CI: 2.5-5.7) for 1-year mortality^[49]. Impaired microvascular perfusion, assessed angiographically using the TIMI myocardial blush grade, also predicts 1-year mortality, which rises from 1.4% in patients with normal blush to 6.2% in patients with absent blush^[50]. Patients with no-reflow have a higher incidence of arrhythmia, remodelling, HF and mortality^[21].

Recent attempts to categorise no-reflow have focused on the upstream causes, including distal embolisation of thrombus, new thrombus formation mid-procedure, and intraprocedural stent thrombosis, collectively badged as intraprocedural thrombotic events (IPTE). The incidence of IPTE was 12.2% in a recent STEMI cohort, with each IPTE component independently associated with 30-d death and MACE^[51]. Beyond angiography, invasive hemodynamic measurement in the cath lab can provide further risk stratification: Measurement of LV end-diastolic pressure is an independent predictor of mortality at 2 years, even after adjustment for baseline LV function^[52].

Coronary physiology

Invasive coronary physiology provides a highly sensitive readout of microcirculatory function, and has demonstrated significant value in prediction of myocardial recovery after MI. The index of microcirculatory resistance (IMR) is the ratio of distal coronary pressure to the inverse of the mean transit time during maximal hyperaemia. Measured after PPCI, IMR is a predictor of ejection fraction and infarct volume at 3 mo post-MI^[53]. An IMR > 40 is associated with increased risk of death or rehospitalisation for HF (HR = 2.1, $P = 0.034$)^[54]. IMR is now being used as a surrogate endpoint in ongoing trials of aspiration thrombectomy and intracoronary GpIIb/IIIa agents^[55]. Hyperaemic microvascular resistance (HMR), another specific read-out of microcirculatory function, is also predictive of CMR-defined microvascular occlusion (MVO), and impaired local blood flow as measured by PET^[56].

Invasive measurement of coronary flow reserve (CFR), zero-flow pressure (Pzf), and fractional flow reserve (FFR) may also have a role in risk stratification following PPCI. CFR is the ratio of ratio of hyperaemic to resting coronary flow and incorporates both the epicardial and microvascular circulations. In 44 patients undergoing PPCI, the change in CFR between presentation and day 1 post-PPCI was predictive of the degree of myocardial salvage and ejection fraction at 6 mo^[57]. Pzf, derived from pressure-velocity loop analysis, is the distal coronary pressure at which the flow in a coronary artery would theoretically cease and represents extra-vascular compression of the microcirculation by oedema

or haemorrhage. Pzf correlates with HMR, and also predicts residual scar at 6 mo post-MI with an AUC of 0.94^[56,58]. FFR, the ratio of myocardial blood flow at maximal hyperaemia in comparison to normal proximal myocardial flow, is also predictive of adverse outcome, with an FFR of ≤ 0.8 associated with an HR of 3.24 for MACE^[58]. The utility of coronary physiology in day-to-day practice, and the optimal index for HF risk stratification remains to be established.

Imaging

Complimentary imaging modalities are providing increasingly detailed phenotyping of myocardial injury, function and healing. Standard echocardiographic indices including ejection fraction, LV volumes, wall motion score index, E/E' ratio and right ventricular function provide prognostic information after MI^[59]. More recently, longitudinal and circumferential strain rate have been shown to be predictive of death or hospital admission for HF, with longitudinal strain rate adding significant incremental value in the prediction of all-cause mortality beyond clinical variables, LVEF, and wall motion score index^[60].

Cardiac MRI offers a broad armamentarium for tissue and functional characterisation, including quantification of the area at risk, infarct size, salvage index, microvascular obstruction, haemorrhage, heterogeneity and scar. Several indices are independently predictive of late outcome, including CMR-determined infarct size, myocardial salvage index and extent of microvascular obstruction^[61-63]. In a study of 249 patients, CMR measurement of MVO was the strongest predictor of MACE over a 6-year follow-up^[64,65]. CMR characterisation of infarct core characteristics, including identification of infarct haemorrhage (by T2W and T2*) or native T1 signal, are recently-described predictors of adverse remodelling and clinical outcome^[66-68].

Combining metabolic imaging by ¹⁸F-fludeoxyglucose (¹⁸F-FDG) with MRI has the potential to provide further characterisation of myocardial injury and repair. ¹⁸F-FDG accumulates in monocyte-macrophages and other highly metabolically active tissues^[69]. In a study of 49 patients hybrid ¹⁸F-FDG PET-MRI was performed at a median 5 d following MI. The intensity of ¹⁸F-FDG signal correlated with infarct size and predicted cardiac function at 6-9 mo follow-up. Interestingly, FDG signal remained an independent predictor after multivariate analysis, providing the first clue that imaging of inflammatory response can be used to risk stratify patients^[70]. Recently, PET imaging of CXCR4, a receptor expressed on leucocytes and haematopoietic stem cells was demonstrated in human patients after MI. This type of approach holds great potential for understanding the biological heterogeneity in the healing response *in vivo*^[71].

Biomarkers

Cardiac biomarkers such as troponin and BNP have established core use for the diagnosis of MI and HF,

and also demonstrate prognostic value for long-term outcome^[72]. A recent study shows that combining serial measurement of traditional biomarkers (e.g., NT-proBNP, hs-cTnT, aspartate transferase, alanine transaminase, lactate dehydrogenase and high-sensitivity C-reactive protein) gives an area under the curve of 0.85 for prediction of LV remodelling^[73]. Looking forward, the field needs biomarkers which define specific biological groups at risk of HF who can be targeted with novel therapeutic agents. These might include biomarkers of inflammation, persistent fibrosis or matrix remodelling. There are data which highlight the potential value of measuring the inflammatory cascade for risk stratification: For example, the ratio of neutrophil:lymphocyte count predicts mortality after NSTEMI and STEMI, which may reflect the functional transition from inflammation to repair^[74,75].

There are a number of emerging potential biomarkers for future HF, including tenascin-C, myeloperoxidase, cytokines, matrix metalloproteinases and growth factors^[76]. Tenascin-C is an extracellular matrix glycoprotein which is not normally expressed in the heart, but is upregulated following MI, or in myocarditis. In patients with acute MI, peak tenascin-C level measured at day 5 is independently predictive of LV remodelling, HF and MACE, and provides additive value to TIMI score and BNP^[77,78]. Copeptin, the C-terminal portion of proavopressin, was the strongest marker of HF after MI from the OPTIMAAL study: A doubling of copeptin was related to a 1.83 fold (1.26-2.64) increased risk of mortality ($P < 0.0001$)^[79,80]. Galectin-3 has shown some promise as a marker of matrix and fibrosis, but has not been found to be an independent predictor of LV remodelling^[81].

CONCLUSION

HF remains a major challenge after MI. Despite the difficulties of interpreting incidence over time, HF indisputably drives much of the late mortality after successful revascularisation and therapeutic interventions to prevent HF in patients at high risk would be hugely valuable. Trials would be facilitated by consensus definitions for HF events and imaging endpoints (e.g., oedema, myocardial salvage and remodelling). Given the long follow-up required for HF events, use of surrogate markers of HF risk (e.g., IMR) could be used for early translational studies. To date, despite an attractive window of opportunity to target myocardial healing, therapies in this field have failed to translate. In part this may reflect divergent mechanisms of HF in different patients, with varying contributions from microcirculatory dysfunction, inflammation, haemorrhage, oedema and remodelling. Coronary physiology and CMR imaging can be used to identify discrete subsets of patients, for example those with MVO, for targeted therapies. For risk stratification, the optimal combination of predictive modalities needs to be defined. Looking ahead, there are three key questions: What is the risk of downstream HF, what mechanisms can be identified, and what therapies

can we trial?

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Transcervical access, reversal of flow and mesh-covered stents: New options in the armamentarium of carotid artery stenting

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Abstract

In the last 25 years, the very existence of carotid artery stenting (CAS) has been threatened on a number of occasions. The initial disappointing results that even lead to the discontinuation of an early randomized controlled trial have improved considerably with time. Novel devices, advanced stent and equipment technology, alternative types of access and several types of filters/emboli protecting devices have been reported to reduce stroke/death rates during/after CAS and improve CAS outcomes. The present review will provide a description of the various technology advances in the field that aim to reduce stroke and death rates associated with CAS. Transcervical access, reversal of flow and mesh-covered stents are currently the most promising tools in the armamentarium of CAS.

Key words: Carotid artery stenting; Stroke; Carotid artery stenosis; Filters

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Core tip: Carotid artery stenting (CAS) has improved considerably in the last few years. This comprehensive review provides the various technology advances in the field that aim to reduce stroke and death rates after CAS. These include transcervical access, reversal of flow and mesh-covered stents.

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INTRODUCTION

During its evolution, carotid artery stenting (CAS) has often gone through some difficult times. One of the first randomized controlled trials comparing CAS with carotid endarterectomy (CEA), the Leicester trial, had to be stopped prematurely after randomizing less than 20 patients^[1]. All 10 patients that were randomized to CEA proceeded without complications. On the other hand, 5 of the 7 patients who were randomized to CAS suffered a stroke ($P = 0.0034$), three of which were disabling at 30 d^[1].

Fortunately, CAS outcomes have improved considerably since then and continue to improve constantly. Technological advances such as proximal/distal embolic protection devices (EPDs), flow reversal, transcervical/transradial access and double layer mesh stent technology are adjuncts that have been developed to improve CAS outcomes. The current article presents an overview of these technological advances.

EPDS

Proximal and distal EPDs are commonly utilized with CAS with the aim of preventing atherosclerotic debris from embolizing to the brain. Catheter manipulation within the aorta and supra-aortic arteries causes plaque embolization. Up to 90% of CAS procedures can be complicated by embolic events and EPDs may capture these embolized particles^[2]. Although some studies report good outcomes for various distal EPDs (also known as filtering devices)^[3-5], others studies argue that distal filters may not be able to prevent all perioperative emboli^[6-9]. The pore size of most available filter devices is $> 80 \mu\text{m}$ ^[3], but many emboli are $< 80 \mu\text{m}$ in size^[10,11]. Furthermore, due to the rigidity of many filter devices and a required minimal distal landing zone depending on the length of the basket of the filter device, the vessel wall apposition may not be optimal (especially in tortuous vessel segments) and could therefore allow cerebral embolization^[12]. These studies have supported that, compared with distal EPDs, proximal EPDs reduce the perioperative microembolic signals detected by transcranial Doppler and the number of new ischemic lesions^[6-9].

A study from Milan, Italy compared the rate of cerebral microembolization during CAS with a proximal EPD [Mo.Ma system (Invatec, Roncadelle, Brescia, Italy); $n = 26$] vs distal protection with a filter [FilterWire EZ (Boston Scientific Corporation, Santa Clara, California); $n = 27$] in patients with high-risk, lipid-rich plaques^[7]. Compared with use of the FilterWire EZ, the Mo.Ma system significantly reduced mean microembolic signal counts during lesion crossing (mean: 18 vs 2, respectively; $P < 0.0001$), stent crossing (mean: 23 vs 0, respectively; $P < 0.0001$), stent deployment (mean: 30 vs 0, respectively; $P < 0.0001$), stent dilation (mean: 16 vs 0, respectively; $P < 0.0001$) and total microembolic signals (mean: 93 vs 16, respectively; P

< 0.0001)^[7].

The Mo.Ma proximal EPD is a safe and effective neuro-protection system during CAS that achieves very low periprocedural stroke rates. A registry of 1300 patients undergoing CAS using the Mo.Ma device reported very low major adverse cardiac or cerebrovascular events including 5 deaths (0.38%), 6 major strokes (0.46%), 5 minor strokes (0.38%) and 0 myocardial infarctions (MIs)^[13]. The incidence of postprocedural events did not increase even in the presence of theoretical anatomical contraindications to proximal endovascular occlusion (e.g., contralateral carotid occlusion). The excellent results reported for the Mo.Ma device suggest that it is a promising technique for the achievement of low stroke rates after CAS.

A prospective randomized study, the Prevention of Cerebral Embolization by Proximal Balloon Occlusion Compared to Filter Protection During Carotid Artery Stenting study, compared the embolic load of filter-protected ($n = 31$) vs proximal balloon-protected CAS ($n = 31$)^[9]. Proximal balloon occlusion lead to a considerable reduction in the percentage of new cerebral ischemic lesions (45.2% vs 87.1%, for proximal balloon occlusion vs filter protection, respectively; $P = 0.001$). Proximal balloon occlusion reduced both the number [median (range): 2 (0-13) vs 0 (0-4); $P = 0.0001$] and the volume [0.47 (0-2.4) cm^3 vs 0 (0-0.84) cm^3 ; $P = 0.0001$] of new cerebral ischemic lesions. Furthermore, contralateral hemisphere lesions were detected in 29.0% vs 6.5% of patients receiving a filter vs balloon occlusion, respectively ($P = 0.047$). Finally, the 30-d major adverse cardiovascular and cerebral events rate was 3.2% for filter protection vs 0% for balloon occlusion, respectively ($P = \text{not significant}$)^[9].

A meta-analysis ($n = 8$ studies; 357 patients) evaluated and compared the results of filter cerebral protection vs proximal balloon occlusion in preventing embolization during CAS as evaluated by diffusion-weighted magnetic resonance imaging (DW-MRI)^[14]. The incidence of new ischemic lesions after CAS/patient detected by DW-MRI (effect size: -0.43; 95%CI: -0.84 to -0.02; $I^2 = 70.08$; $Q = 23.40$) and the incidence of contralateral site lesions (effect size: -0.50; 95%CI: -0.72 to -0.27; $I^2 = 0.00$; $Q = 3.80$) were both significantly lower in the proximal balloon occlusion group^[14]. The results of this meta-analysis support the superiority of proximal balloon occlusion as compared with filter cerebral protection with respect to the degree of CAS-related brain embolization^[14].

Others, however, have supported that proximal EPDs have similar results with distal filter EPD^[15]. The lack of difference in proximal occlusion vs distal filter EPD results was also verified in a meta-analysis^[16]. This meta-analysis included 7 studies ($n = 392$ patients; 193 with proximal occlusion; 199 with distal filters). The use of proximal occlusion vs distal filter did not reduce the risk of new cerebral lesions (OR = 0.65; 95%CI: 0.28-1.52; $P = 0.32$) or the risk of death/cerebrovascular event (OR = 0.59; 95%CI: 0.22-1.60; $P = 0.30$)^[16]. A more

recent meta-analysis verified the equipoise in clinical outcomes between proximal balloon occlusion and distal filter protection^[17]. This meta-analysis ($n = 18$ studies; 12281 patients) did not demonstrate any significant difference between the two modalities in terms of the risk of stroke or mortality, nor was there any difference in the incidence of new cerebral lesions on DW-MRI or contralateral DW-MRI lesions. The conclusion reached was that both proximal and distal EPDs provide similar levels of protection from periprocedural stroke and 30-d mortality^[17]. Finally, a national cardiovascular data registry analysis from the United States compared stroke/death rates between proximal EPDs and distal filter EPDs in 10,246 consecutive elective CAS procedures. Both EPDs were associated with similar 30-d adverse event rates (2.7% vs 4.0%, after proximal vs distal filter EPDs, respectively; $P = 0.22$)^[18].

TRANSCERVICAL ACCESS WITH FLOW-REVERSAL

The first description of flow reversal as a cerebral protection device was in 2000^[19]. Although initially CAS with flow reversal was performed *via* the transfemoral approach^[19], a subsequent modification was the use of transcervical approach for CAS with flow reversal^[20]. This technique is described in detail elsewhere^[20]. Several independent studies have published very low 30-d stroke/death/MI rates and low incidence of complications for transcervical CAS with flow reversal^[21-25]. It was recently demonstrated that transcervical CAS with flow reversal demonstrates embolization rates comparable with CEA^[26]. Transcervical CAS with flow reversal thus seems a promising method for the reduction of strokes associated with CAS^[27].

Elderly patients (> 70 years) have inferior outcomes with transfemoral CAS compared with CEA^[28]. The poor outcome of transfemoral CAS in this age group may be explained by the anatomic characteristics of the aortic trunk and supra-aortic vessels as well as by a high prevalence of aortic arch atheromatosis^[21]. Transcervical CAS with flow reversal for cerebral protection avoids these unfavorable characteristics. An early study reported a 2.2% 30-d combined stroke/death/MI rates in 219 patients > 70 years of age (55.7% asymptomatic; 44.3% symptomatic)^[21]. Symptomatic patients had a 5.1% combined stroke/death/MI rates whereas asymptomatic patients had a 0% rate^[21]. Thus, transcervical CAS with flow reversal may be the preferred option for this age group.

Not long ago, the Reverse Flow Used During CAS Procedure (ROADSTER) multicenter trial reported its results from the evaluation of the safety and efficacy of the ENROUTE Transcarotid NPS (Silk Road Medical Inc, Sunnyvale, Calif), a novel transcarotid neuroprotection system that provides direct surgical common carotid access and cerebral embolic protection *via* high-rate flow reversal during CAS^[29]. This study reported an

overall stroke rate of 1.4%, which is the lowest reported for any prospective multicenter clinical trial of CAS. The stroke/death rates (2.8%) and the stroke/death/MI rates (3.5%) reported were also similarly low^[29].

Direct percutaneous carotid access is an alternative access that has been described for CAS. This access can be used in individuals with difficult anatomies, high-risk patients and certain emergent situations that warrant easy and rapid access to the CCA^[30]. A systematic review ($n = 12$ studies; 739 CAS procedures) showed that direct CAS with transcervical access (filter protected or unprotected; $n = 250$ patients) and CAS with transcervical access under reversed flow (with arteriovenous shunt in most cases; $n = 489$ patients) are both associated with a low incidence of stroke and complications^[31]. The incidence of stroke, MI and death was 1.1%, 0.14% and 0.41%, respectively. The incidence of stroke was 1.2% (3 of 250) in direct CAS with transcervical access and 1.02% (5 of 489) in CAS under reversed flow ($P =$ not significant). Transient ischemic attack occurred in 20 patients (2.7%)^[31].

HEAD-TO-HEAD COMPARISON/ COMBINATION OF STRATEGIES

Several studies have compared/combined the various proposed adjuncts to improve CAS outcomes in an attempt to identify those measures that would help improve CAS results to a greater extent. A study from Argentina compared transradial vs transfemoral CAS^[32]. A total of 775 consecutive patients undergoing CAS during 16 years were included (101 transradial vs 674 transfemoral). The primary combined end-point was in-hospital major adverse cardiac and cerebral events, whereas secondary end-points included angiographic outcome after the procedure and cross-over rate to another puncture site. Angiographic success was achieved in all 775 patients. There was a significant difference in cross-over rate (4.9% vs 0%, for the transradial vs the transfemoral approach, respectively; $P < 0.05$), but not in the incidence of in-hospital major adverse cardiac and cerebral events (2% vs 3.6%, for the transradial vs transfemoral approach, respectively; $P =$ not significant)^[32]. It was concluded that both approaches are safe and efficacious. These results verified the results of an earlier study^[33].

An earlier study from Atlanta, Georgia, United States compared revascularization outcomes after CEA ($n = 226$) vs CAS with a distal filter EPD ($n = 216$) vs CAS with a proximal flow reversal system ($n = 53$)^[34]. The 3 groups did not differ in the overall composite end-point of death, cerebrovascular accident and MI (4% vs 5.1% vs 0%, respectively; $P = 0.1$) or any individual major adverse event^[34]. Overall, patients undergoing CAS with EPD had a greater incidence of minor cerebrovascular accidents than CEA patients (6 vs 1, or 3.4% vs 0.5%, respectively; $P = 0.031$). This was driven by the increased risk for a cerebrovascular accident for

asymptomatic patients. Of note, patients undergoing CAS with flow reversal ($n = 53$) had zero adverse events (minor/major stroke, MI or death)^[34].

A study from Japan evaluated the effectiveness of the combined use of distal filter protection device [FilterWire EZ (Boston Scientific, Natick, MA)] and the Mo.Ma Ultra (Medtronic, Minneapolis, MN)^[35]. The Mo.Ma Ultra is an EPD for interrupting the antegrade blood flow to the internal carotid artery. This study demonstrated that the combined use of a distal filter protection device and Mo.Ma Ultra could provide a more reliable embolic protection in CAS^[35].

A study from Italy reported the outcomes of 214 patients undergoing CAS *via* a transradial ($n = 154$) or a transbrachial ($n = 60$) approach with either the Mo.Ma proximal protection ($n = 61$) or the distal filter protection ($n = 163$)^[36]. As a result of technical difficulties in catheterizing the target vessel, crossover to a femoral approach was required in 11 of 153 (7.1%) filter patients, but only in 1 of the 61 (1.6%) Mo.Ma patients. On the other hand, 5 Mo.Ma patients developed acute intolerance to proximal occlusion (4 were subsequently shifted to filter protection). One patient undergoing CAS *via* the transradial approach was shifted to filter because the Mo.Ma system was too short. Overall, CAS was technically successful in 55 of the 60 (90%) Mo.Ma patients and in 142 of the 154 (93%) filter patients. The 30-d major adverse cardiovascular/cerebrovascular events rate did not differ significantly between the 2 groups (0% for Mo.Ma patients vs 2.8% for filter patient; $P = 0.18$). There was similarly no difference in radiation exposure between the 2 groups. Major vascular complications occurred in 1 of the 61 (1.6%) Mo.Ma patients and in 3 of the 153 (1.96%) filter patients, respectively ($P = 0.18$). All these complications occurred during the early learning phase of the transbrachial approach. After a mean follow-up of 8.1 ± 7.5 mo, chronic radial artery occlusion was detected by Doppler ultrasound in 2 of the 30 (6.6%) Mo.Ma patients and by clinical assessment in 4 of 124 (3.2%) filter patients ($P = 0.25$). The conclusion reached was that CAS with proximal protection *via* a transradial or a transbrachial approach is a safe, feasible and effective technique with low rate of vascular complications^[36].

A study from Japan compared the effectiveness of the embolization prevention mechanism of 2 types of EPDs - a distal protection balloon ($n = 82$ patients) and a distal protection filter ($n = 82$ patients)^[37]. Positive findings on postoperative diffusion-weighted imaging were found in more patients with distal protection balloon compared with the distal protection filter (34 vs 22 patients, or 41.4% vs 26.8%, respectively). Furthermore, in the distal protection balloon group there were more strokes than in the distal protection filter group (2 minor and 2 major strokes vs 0 strokes, respectively)^[37]. A combination of flow reversal and distal filter may be more effective than either modality alone^[38].

Controversial results were reported in a small study from Brazil^[39]. This study compared flow reversal vs filter protection in 40 patients undergoing CAS using a femoral approach. Compared with flow reversal ($n = 21$), filter protection ($n = 19$) resulted in a reduction in the incidence (15.8% vs 47.6%, respectively; $P = 0.03$), number (0.73 vs 2.6, respectively; $P = 0.05$) and size (0.81 mm vs 2.23 mm, respectively; $P = 0.05$) of new ischemic brain lesions^[39]. Flow reversal was associated with a tendency toward increased incidence of ipsilateral ischemic lesions more than those who had filter protection (70% vs 0.0%, respectively; $P = 0.07$). In addition, flow reversal showed a greater tendency toward increased incidence of ipsilateral lesions than bilateral (70% vs 30%, respectively; $P = 0.07$)^[39]. As the authors mentioned, this trial was the first to show better results using filter protection than a proximal protective technique during CAS. The authors attributed these good results to their considerable operator experience with CAS, the general anesthesia (which minimized the risk of movement accidents) and to the filter protection device profile^[39].

ADVANCES WITH STENT DESIGN

Several important advances in stent design have also lead to improved CAS outcomes. For instance, the Inspire MD technology (Tel Aviv, Israel) includes a bare-metal stent (Inspire MD C-Guard stent) covered by a micron level mesh (MicroNet). Preliminary results appear encouraging^[40]. A prospective multicenter study, the C-Guard CARotid Embolic protection using microNET trial evaluated the feasibility of the C-Guard carotid embolic protective stent system^[41]. This is a novel thin-strut nitinol stent combined with a polyethylene terephthalate mesh covering. This study reported a 0% 30-d major adverse cardiac or cerebrovascular events rate in 30 patients^[41]. Another stent that has demonstrated promising results is the double-layer CASPER-RX stent^[42]. Finally, the Roadsaver Micromesh stent is a novel nitinol double-layer micromesh stent. Preliminary results from high-volume centres showing a low incidence of embolic events and new ipsilateral ischemic brain lesions are encouraging^[43,44].

During CAS, debris is often trapped in stent interstices. When flow is restored following CAS, the trapped debris may prolapse through the stent struts and result in delayed cerebral embolization^[45]. Three companies (Roadsaver™ Micromesh Carotid Stent, Terumo, Japan; C-Guard™ MicroNet-Covered Embolic Prevention Stent System, InspireMD, Boston, MA, United States; and Scaffold Stent, W.L. Gore and Associates, Flagstaff, AZ, United States) are evaluating membrane or mesh covered carotid stents with smaller interstices to prevent such delayed strokes^[45].

The advances in carotid stent material and the new types of stents introduced in the market are beyond the scope of this review and are more extensively described elsewhere^[46].

CONCLUSION

The battle for CAS is not lost^[47]. The long-term results of the Carotid Revascularization Endarterectomy vs Stenting Trial did not show a significant difference in periprocedural stroke, MI or death and subsequent ipsilateral stroke between symptomatic and asymptomatic patients undergoing CAS or CEA^[48]. Similarly, the Asymptomatic Carotid Trial demonstrated non-inferiority for CAS compared with CEA for asymptomatic patients with respect to the primary composite end-point of 30-d death, stroke or MI and ipsilateral stroke within 1 year^[49]. New devices, membrane- and mesh-covered stents, alternative approaches and a combination of EPDs are tools in the armamentarium of CAS to improve its results. There is more to see in the future and we will all be awaiting the results of new trials incorporating the advances in CAS technology.

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Empirical anticoagulation for patients in sinus rhythm at high risk of ischaemic stroke: A review of current literature

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Abstract

Ischaemic stroke is one of the commonest causes of morbidity and mortality worldwide and around a fifth of events can be attributed to a cardioembolic source. This is typically due to atrial fibrillation (AF), the most common sustained cardiac arrhythmia. However, AF can, at times, be difficult to detect due to a relative lack of symptoms and the fact that it can be paroxysmal in nature. Studies have shown that diagnosis of AF improves as the length of cardiac monitoring increases. However, prolonged cardiac monitoring is not a cost-effective way of diagnosing AF. Therefore, an alternative approach may be to empirically anticoagulate individuals who are at high risk of stroke. This article summarises current evidence surrounding stroke risk prediction, the use of anticoagulation in the secondary prevention of stroke and its use in the primary prevention of stroke in high risk groups with the aim of determining whether empirical anticoagulation is a safe and effective strategy.

Key words: Anticoagulation; Ischaemic stroke; Atrial fibrillation; CHA₂DS₂VASc; CHADS₂; Heart failure; Coronary artery disease; Peripheral arterial disease

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Core tip: This is a contemporary review exploring issues related to the risk of stroke and use of anticoagulation in patients who are in sinus rhythm (SR). It examines the prediction of stroke in patients without known atrial fibrillation (AF), the identification of AF in patients following stroke and the use of anticoagulation in post-stroke patients seemingly in SR or those at high-risk of stroke. The main findings are: (1) prolonged cardiac monitoring increases the rate of AF diagnosis but is not cost-effective; (2) current risk stratification schemes such as CHA₂DS₂VASc can identify those in sinus rhythm who are at risk of stroke; and (3) further research is required to determine whether individuals at high-risk of stroke would benefit from anticoagulation.

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INTRODUCTION

Ischaemic stroke is a leading cause of morbidity and mortality worldwide^[1] and, following a first event, around a quarter of patients will go on to have a recurrent stroke^[2,3]. Atrial fibrillation (AF), a common cause of stroke, is the most common sustained cardiac arrhythmia with an estimated prevalence approximately 3% in adults aged 20 years or older^[4], a figure that is expected to double over the next 50 years^[5]. This arrhythmia carries a five-fold risk of stroke and patients who experience an AF-related stroke often suffer the most severe forms of the condition^[6].

Risk scores such as CHADS-2 and, more recently, CHA₂DS₂VASc have been developed in order to identify those patients with AF and an increased risk of stroke who would potentially benefit from anticoagulation. However, these risk scores are currently used only in patients with a confirmed diagnosis of AF, a condition which is underdiagnosed due to the fact it can be asymptomatic and paroxysmal. Therefore, given that 45% of all AF-related strokes occur in patients with previously undetected AF^[7], many more patients could potentially benefit from empirical anticoagulation therapy and there may be a role for using these risk scores in patients without known AF but with risk factors for developing stroke.

In view of the fact that AF can be difficult to detect, a number of studies have attempted to determine whether it is appropriate to give empirical anticoagulation to patients in sinus rhythm (SR) with risk factors for stroke. This article aims to summarise these studies and determine whether there are clinically relevant scenarios where anticoagulating patients in SR may be appropriate to reduce their risk of stroke.

LITERATURE SEARCH AND METHOD

A Medline and Embase search was performed in August 2016 using the following terms: CHADS-2, CHA₂DS₂VASc, anticoagulation, vitamin K antagonist, warfarin, Coumadin, novel oral anticoagulant, direct oral anticoagulant, apixaban, eliquis, dabigatran, pradaxa, rivaroxaban, xarelto, edoxaban, lixiana, sinus rhythm, non-atrial fibrillation, normal heart rhythm, "without atrial fibrillation", stroke, cerebrovascular accident, cerebrovascular event, transient ischaemic attack (TIA), mini-stroke, heart failure, cardiac failure, left ventricular failure, left ventricular impairment, left ventricular dysfunction, impaired ventricle, coronary artery disease,

coronary heart disease, myocardial ischaemia, myocardial infarction, acute coronary syndrome, peripheral arterial disease and peripheral vascular disease.

STROKE RISK PREDICTION IN A GENERAL POPULATION WITHOUT AF

In patients without known AF, risk assessment tools currently focus on overall cardiovascular risk rather than determining their specific risk of stroke. However, could risk scores such as CHADS-2 and CHA₂DS₂VASc be used within this patient group to determine their cerebrovascular event risk?

An analysis of the Chin-Shan Community Cohort Study tested a number of risk stratification schemes which are currently used to predict thromboembolic risk in AF, including CHADS-2 and CHA₂DS₂VASc, in a Chinese population without known AF^[8]. This showed a modest predictive value of these risk stratification schemes in predicting stroke in non-AF patients with a C-statistic value ranging from 0.658 to 0.728, values which were broadly similar to those seen in an exploratory analysis of patients with AF within the same community.

Similar results were found in a meta-analysis performed by Santos *et al* who examined the use of the CHADS-2 score at predicting cerebrovascular events^[9]. They found that CHADS-2 was able to identify patients at risk of stroke, regardless of whether AF was present or not.

More recently, Saliba *et al*^[10] assessed the performance of CHADS-2 and CHA₂DS₂VASc within a large Israeli population over a three year follow-up period. In individuals without AF, the C-statistic values were 0.718 and 0.714 for CHADS-2 and CHA₂DS₂VASc respectively and in individuals with AF, the C-statistic values were 0.606 and 0.610 respectively. The authors concluded that these risk tools had a relatively high performance at predicting thromboembolism in patients without AF.

In all of these studies, the results suggest that current risk stratification schemes used in AF patients to predict thromboembolism could also be used in patients without AF as a screening tool to predict their risk of stroke. It remains unclear, however, as to whether anticoagulating these patients is a superior strategy to giving antiplatelet therapy.

SECONDARY PREVENTION OF ISCHAEMIC STROKE/TIA

Around a fifth of ischaemic strokes are cardioembolic in origin^[11] and these patients typically receive oral anticoagulants to reduce their risk of future events. However, around a third of ischaemic strokes are termed cryptogenic^[12], or without an attributable cause despite extensive work-up. The majority of these cases are likely to have an embolic mechanism and a significant proportion are likely to be related to undiagnosed AF.

Table 1 Randomised control trials which show an increased yield of atrial fibrillation detection with extended cardiac monitoring

Ref.	Design	No. of patients	Inclusion/exclusion criteria	Type of monitoring	Outcome	Comments
Higgins <i>et al</i> ^[14] (2013)	RCT	100	Inclusion: Ischaemic stroke within 7 d; Exclusion: History of AF	7-d event recorder <i>vs</i> 24-h ECG (control)	Detection of AF: Sustained (> 20 s) and non-sustained (minimum 6 beats)	Sustained AF detected in 18% (control 2%); Non-sustained AF in 44% (control 4%)
Gladstone <i>et al</i> ^[15] (2014)	RCT	572	Inclusion: Cryptogenic stroke, Age ≥ 55 yr; Exclusion: History of AF	30-d triggered event recorder <i>vs</i> 24-h ECG (control)	Detection of AF (> 30 s)	AF detected in 16.1% (control 3.2%)
Sanna <i>et al</i> ^[16] (2014)	RCT	441	Inclusion: Cryptogenic stroke, Age ≥ 40 yr;	Insertable cardiac monitor <i>vs</i> Standard care (control)	Detection of AF (> 30 s)	At 6 mo, AF detected in 8.9% (control 1.4%) At 12 mo, AF detected in 12.4% (control 2.0%)
Brachmann <i>et al</i> ^[17] (2016)			Exclusion: History of AF (including 24-h ECG)			At 36 mo, AF detected in 30% (control 3.0%)

AF: Atrial fibrillation; RCT: Randomized controlled trial.

Ziegler *et al*^[13] analysed data from patients at risk of thromboembolism (stroke/TIA) who had implantable cardiac devices capable of recording atrial arrhythmias. They identified newly detected episodes of atrial fibrillation/tachycardia in 28% of patients over a 1-year follow-up period.

Multiple studies have shown that the yield of detecting AF increases as the length of ambulatory monitoring increases (Table 1)^[14-17]. A systematic review and meta-analysis performed by Dussault *et al* assessed the relationship between the duration of ECG monitoring and the incidence of AF detection in patients who had suffered a cerebrovascular event, using data from 31 studies^[18]. They found that extending monitoring from 24 h to 30 d improved AF detection from 4.38% to 15.2% and if this monitoring was extended out to 180 d, detection rates increased to 29.15%.

Studies have also shown that in patients with implantable electronic devices, asymptomatic episodes of AF can be associated with an increased risk of thromboembolic events^[19-25], with a hazard ratio ranging from 2.2 to 9.4^[26]. The length of each episode that is required to increase overall stroke risk varies in these studies, from a minimum of 5 min in the Ancillary MOde Selection Trial^[19] to a maximum of 24 h in the Italian AT500 Registry^[20]. At present, the episode duration and burden of asymptomatic AF that best predict future thromboembolic events are still matters of debate and need to be addressed by future studies.

A more recent systematic review performed by the Canadian Agency for Drugs and Technologies in Health examined not only the clinical effectiveness of cardiac monitoring in patients who had recently experienced a stroke or TIA, but also the cost effectiveness^[27]. They showed that there was a substantial increase in the detection of AF when monitoring was performed for more than 24 h. Monitoring beyond 30 d increased this detection further although these improvements were modest. From an economic point of view, they

concluded that in patients who were admitted with a cerebrovascular event and did not receive in-patient continuous cardiac monitoring, 7 d cardiac monitoring was likely to identify significantly more cases of AF compared with current 24 h monitoring, with an acceptable increase in cost [CAN\$ 50000-80000/QALY (£ 28000-46000/QALY) gained]. Cost-effectiveness could be improved further by targeting stroke survivors who were relatively healthy and in whom there was a higher suspicion of underlying AF. However, they also concluded that extending monitoring beyond 7 d was unlikely to be cost-effective [CAN\$ 85000/QALY (>£ 49000/QALY) gained].

Current guidance continues to recommend long-term cardiac monitoring in patients who have a stroke with an undiagnosed cause with the AHA/ACC/HRS specifying at least 30 d. In view of the fact that this may not be cost-effective, would it be more appropriate to use current risk stratification schemes to identify those patients who may be at risk of further cerebrovascular events?

A trial by Ntaios *et al*^[28] examined whether CHADS-2 and CHA₂DS₂VASc scores could be used to predict long-term outcomes in non-AF stroke patients. They divided patients into low, intermediate or high risk sub-groups, dependent upon their pre-stroke CHADS-2 and CHA₂DS₂VASc score. In both the CHADS-2 and CHA₂DS₂VASc sub-groups, they found that there were significant differences in stroke recurrence, cardiovascular events and 5-year mortality. They also demonstrated that compared with the low-risk sub-group, patients in the high-risk sub-group had a higher risk of stroke recurrence [CHADS-2, hazard ratio (HR): 1.71; CHA₂DS₂VASc, HR: 2.93]. These results suggest that current clinical risk scores can be used to predict future events in patients who have had a stroke or TIA.

To improve the accuracy of these risks scores in post-stroke patients further, modification of certain variables may be helpful. Thijs *et al*^[29] assessed

patients who had suffered a cryptogenic stroke or TIA and had an insertable cardiac monitor to determine whether there were specific factors which could predict the development of AF in this population. Following multivariate analysis, they found that increasing age [HR per decade 1.9 (1.3-2.8), $P = 0.0009$] and PR interval prolongation [HR per 10 ms: 1.3 (1.2-1.4), $P < 0.0001$] were independently associated with an increased incidence of AF. Therefore, in non-AF stroke/TIA patients, the addition of PR interval duration and placing further emphasis on age may help improve the accuracy of current risk scores.

Nevertheless, despite the fact that CHADS-2 and CHA₂DS₂-VASc may help to predict future events in non-AF stroke/TIA patients, more evidence is required to determine whether those within an intermediate or high-risk group should be offered anticoagulation.

PRIMARY PREVENTION OF ISCHAEMIC STROKE/TIA IN SPECIFIC GROUPS

Heart failure

It has long been established that heart failure (HF) is associated with an increased risk of thromboembolism and in particular, stroke. A systematic review performed by Witt *et al* analysed stroke rates in heart failure patients and found the risk of stroke to be 1.8% in the first year of HF diagnosis, rising to 4.7% at 5 years^[30]. Multiple studies have attempted to clarify whether HF patients in SR would benefit from anticoagulant therapy. Initial trials suffered from poor recruitment and underpowered results and so it is not surprising that they failed to demonstrate an overall benefit of anticoagulation in this population^[31-33]. One of these studies, the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial, did however show a significant reduction in non-fatal ischaemic strokes in patients on warfarin compared with aspirin or clopidogrel ($P < 0.01$)^[33]. This was at the expense of a higher rate of major bleeding events.

More recently, the Warfarin vs Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial compared warfarin and aspirin in patients with HF in SR, using the primary endpoints of ischaemic stroke, intracerebral haemorrhage or death from any cause^[34]. Although there was no overall difference in the combined primary endpoints between the two treatments ($P = 0.4$), warfarin was associated with a significant reduction in the rate of ischaemic stroke (2.5% vs 4.7%, $P = 0.005$) without a significant difference in the rate of intracerebral or intracranial haemorrhage ($P = 0.82$). Once again, the rate of major bleeding was higher (warfarin 5.8% vs aspirin 2.7%, $P < 0.001$).

One limitation of the WARCEF study was the time in therapeutic range (TTR) among patients in the warfarin group which was relatively low at 63% (high-quality warfarin treatment is defined as a TTR > 70%^[35]). Low TTRs are strongly associated with adverse outcomes

such as major haemorrhage and thromboembolic events^[35]. The higher bleeding risk with warfarin may, in part, be related to this low TTR. One solution to this could be use of direct oral anticoagulants (DOACs) which, in the absence of compliance issues, provide a much more consistent level of therapeutic anticoagulation. DOACs have already been shown to be non-inferior, and in some cases, superior to warfarin with respect to stroke and major bleeding risk reduction^[36-39]. Further research exploring the use of DOACs in HF patients is needed to determine whether they can reduce thromboembolic risk without significantly increasing bleeding risk.

In terms of estimating stroke risk within HF patients without AF, current clinical risk scores have been assessed. A recent prospective cohort study investigated whether CHA₂DS₂-VASc could be used to predict the risk of ischaemic stroke in HF patients without AF^[40]. It performed moderately at predicting ischaemic stroke at 1- and 5-year follow-up (C-statistics 0.67 and 0.69 respectively) and performed well at identifying those at low risk of ischaemic stroke with a negative predictive value of 92%. Additionally, the authors found that those with a CHA₂DS₂-VASc score of ≥ 2 had a stroke risk of > 1% per year. To put this into context, patients with AF are typically offered anticoagulation once their annual stroke risk exceeds 1%. This would suggest that the CHA₂DS₂-VASc score may have a use in identifying those HF patients without AF who are at risk of stroke. Whether these patients would gain benefit from anticoagulation remains to be seen and clinical trials are needed to clarify this.

Coronary artery disease

Coronary artery disease (CAD) has been identified as an independent risk factor for stroke^[41] and co-existent vascular disease, such as coronary or peripheral artery disease, is present in around 40% of stroke patients^[42]. Studies have previously examined the addition of warfarin to antiplatelet therapy in patients with acute coronary syndrome (ACS). These were performed in an era before the widespread use of dual antiplatelet therapy. A meta-analysis of the studies found that the addition of warfarin led to reduction in major adverse cardiovascular events {MACE: death, non-fatal MI, non-fatal ischaemic stroke; [OR = 0.73 (0.63-0.84), $P < 0.0001$]} but this was at the expense of an increased risk of major bleeding [OR 2.32 (1.63-3.29), $P < 0.00001$]^[43]. As a result, anticoagulation is not routinely given to patients following ACS. However, a proportion of these patients will be at significant risk of thromboembolic events and if a clinical risk score could accurately identify this sub-group, they might well benefit from anticoagulation.

A prospective registry study by Mitchell *et al*^[44] assessed the accuracy of CHADS-2 and CHA₂DS₂-VASc at predicting cerebrovascular events in non-AF patients who had suffered an ACS. They found that the incidence of stroke increased with increases in each risk score and

that a CHADS-2 score ≥ 3 or a CHA₂DS₂VASc score ≥ 4 was associated with an annual stroke incidence of $\geq 1\%$. Both CHADS-2 and CHA₂DS₂VASc performed moderately at predicting ischaemic stroke [C-Statistics (0.68 and 0.71 respectively)].

Similar results were found in a prospective cohort study which assessed the accuracy of CHADS-2 at predicting cerebrovascular events in non-AF patients who had stable CAD^[45]. Those with a CHADS-2 score of 2-3 had a 2.7 times higher rate of stroke and those with a CHADS-2 score of 4-6 had a 4.6 times higher rate of stroke. They concluded that stable CAD patients with a CHADS-2 score of 5-6 had a comparable stroke rate to AF patients with a CHADS-2 score of 2-3, the level at which anticoagulation is felt to be beneficial.

In both of these studies, cerebrovascular events occurred despite antiplatelet therapy. They indicate that in patients with CAD, high CHADS-2 or CHA₂DS₂VASc scores can predict those at risk of stroke or TIA. These patients may therefore benefit from the addition of anticoagulation and further studies are required to clarify this.

Peripheral arterial disease

The presence of peripheral arterial disease (PAD) is a significant predictor of stroke and in one study was found to be present in 14.4% of major ischaemic strokes and 8.9% of minor ischaemic strokes^[46]. Warfarin has also been evaluated for the use in this patient group. A meta-analysis which assessed the use of anticoagulation in PAD patients provided inconclusive results^[47] and led to the development of the Warfarin Antiplatelet Vascular Evaluation (WAVE) Trial^[48]. This compared oral anticoagulation plus antiplatelet therapy vs antiplatelet therapy alone. They found no significant difference in MACE events (relative risk: 0.92; 95%CI: 0.73-1.16; $P = 0.48$). However, those receiving combination therapy had a significantly higher rate of major bleeding rate (4.0%), compared with in those receiving antiplatelet monotherapy (1.2%). There is some evidence that patients undergoing vein graft bypass surgery gain benefit from warfarin monotherapy^[49] and this is the only sub-group of PAD patients in which anticoagulation is currently indicated.

To date, there is only one trial which has examined the use of clinical risk scores to predict thromboembolic events in patients with PAD. Yang *et al*^[50] assessed the accuracy of CHADS-2 and CHA₂DS₂VASc in predicting 5-year cumulative ischaemic stroke risk in PAD patients. They found that each increase in the risk scores led to an increased stroke risk, and both scores performed well at predicting 5-year cerebrovascular events (C-statistics 0.92 for CHADS-2, 0.862 for CHA₂DS₂VASc). In multivariate analysis, each increment of the CHADS-2 or CHA₂DS₂VASc score was associated with around a three-fold increase in stroke risk.

As with CAD, current risk scores appear to be able to identify those PAD patients who are at high-risk of cerebrovascular events and this sub-group may also

benefit from anticoagulation therapy. More clinical evidence is required to confirm this.

CONCLUSION

Cerebrovascular disease remains one of the leading causes of death throughout the world. Those that survive are commonly left with serious long-term disability and are at an increased risk of recurrent events. AF is a common cause of stroke/TIA but because the arrhythmia can be paroxysmal and asymptomatic, it remains a challenge to detect. Long-term ambulatory monitoring has not been shown to be a cost-effective way of diagnosing the arrhythmia. Additionally, the duration of AF which represents an increased risk of thromboembolism is still to be determined.

An alternative strategy is to use current risk stratification schemes such as CHADS-2 or CHA₂DS₂VASc. There is evidence to suggest that these scores can identify those at significant risk of thromboembolic events, not only in the general population but more specifically in those that have suffered a cerebrovascular event or have co-existent HF, CAD or PAD.

At present, it remains unclear as to the most appropriate way of treating these high-risk patients once they have been identified. With the dawn of DOACs, which can provide a more steady-state of anticoagulation and potentially have a better bleeding profile, there are now therapeutic options which may benefit high-risk groups. Future trials should use risk scores to identify high-risk groups in a variety of clinical settings to determine whether anticoagulation therapy can reduce the burden of cerebrovascular disease.

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Antitachycardia pacing programming in implantable cardioverter defibrillator: A systematic review

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Abstract

Implantable cardioverter defibrillator (ICD) programming

involves several parameters. In recent years antitachycardia pacing (ATP) has gained an increasing importance in the treatment of ventricular arrhythmias, whether slow or fast. It reduces the number of unnecessary and inappropriate shocks and improves both patient's quality of life and device longevity. There is no clear indication regarding the type of ATP to be used, except for the treatment of fast ventricular tachycardias (188 bpm-250 bpm) where it has been shown a greater efficacy and safety of burst compared to ramp; 8 impulses in each sequence of ATP appears to be the best programming option in this setting. Beyond ATP use, excellent clinical results were obtained with programming standardization following these principles: extended detection time in ventricular fibrillation (VF) zone; supraventricular discrimination criteria up to 200 bpm; first shock in VF zone at the maximum energy in order to reduce the risk of multiple shocks. The MADIT-RIT trial and some observational registries have also recently demonstrated that programming with a widespread use of ATP, higher cut-off rates or delayed intervention reduces the number of inappropriate and unnecessary therapies and improves the survival of patients during mid-term follow-up.

Key words: Implantable cardioverter defibrillator programming; Antitachycardia pacing; Ventricular tachycardia; Electrical antitachycardia therapy

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Core tip: Antitachycardia pacing (ATP) has a great importance in the treatment of ventricular arrhythmias, whether slow or fast. It reduces the number of unnecessary shocks and it improves both patient's quality of life and device longevity. Beyond ATP use, excellent clinical results were obtained with programming standardization following these principles: Extended detection in ventricular fibrillation (VF) zone; supraventricular discrimination criteria up to 200 bpm; first shock in VF zone at the maximum energy in order to reduce the risk of

multiple shocks. The MADIT-RIT trial and some registries have also recently demonstrated that programming with a widespread use of ATP, higher cut-off rates or delayed intervention reduces the number of inappropriate therapies and improves the survival of patients during medium term follow-up.

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INTRODUCTION

The efficacy of implantable cardioverter-defibrillator (ICD) in reducing sudden death and total mortality is well documented^[1], initially in secondary prevention^[2-4], more recently also in primary prevention^[5,6]. In particular, two big trials, MADIT II^[5] and SCD-HeFT^[6], helped to define high risk patients after a myocardial infarction (MI) or with heart failure (HF) associated with reduced left ventricle ejection fraction.

These studies showed that the overall survival rate was higher in patients with ICD compared with those who received conventional medical therapy^[5,6].

In the last decade, ICD implants have grown exponentially^[7], leading manufacturers to heavily invest in this field to improve therapies and develop sophisticated algorithms with high sensitivity and specificity for arrhythmias discrimination. Once detected, the ICD can treat ventricular arrhythmias with high-energy shocks or antitachycardia pacing (ATP).

Although ICDs are usually well accepted by most patients, there are several clinical reports of anxiety and depression after implantation^[8,9]. Quality of life can, in fact, be negatively influenced when receiving painful shocks, especially if multiple^[10]. The main benefit of ATP therapy, from the patient's point of view, is to avoid painful shocks; actually, ATP is rarely noticed by patients and therefore well tolerated. Moreover, battery life of the device is extended if the high-energy shock therapy is avoided. Even more important, it has also been demonstrated that shock therapy is associated with a higher risk of mortality compared to ATP sequences only^[11].

With the increase in ICD indications, the choice of an optimal device programming, both for discrimination and therapy, is becoming increasingly important. A critical analysis of the most important clinical studies in this field is crucial in order to achieve an effective and safe therapy that improves patient's outcome without adversely affecting quality of life.

WHAT IS ATP?

ATP consists of one or more trains of pacing stimuli

(usually 8 impulses for each train) conventionally expressed as a percentage of the tachycardia cycle length for a given RR interval, from the onset of the preceding R wave. Pace stimulation delivered at very short coupling intervals (*i.e.*, < 84%) is more likely to enter a reentrant circuit but also accelerate the arrhythmia. Unlike shock therapy, the locations of the ICD generator and shocking coils do not affect ATP efficacy. ATP is usually delivered from the right ventricular apex (RVA), but efficacy is similar also when pacing from outflow tract. ATP from RVA is less effective in terminating ventricular tachycardia (VT) with a basal exit site^[1].

The rationale for ATP efficacy relies of the fact that monomorphic VT can be interrupted with appropriately timed pacing stimuli delivered into the excitable gap of a reentrant circuit. The chance of arrhythmia interruption depends on several factors: The conduction time from pacing stimulus site to the reentrant circuit; the duration of the excitable gap; the presence of anatomic/functional barriers; the state of the sympathetic nervous system. For example, beta-blockers drugs increase the duration of excitable gap, thus increasing ATP efficacy^[10].

VT with spontaneous RR interval variability are more likely be ATP responsive, while those with greater variation in QRS morphology are less responsive. This is the reason why polymorphic VT and ventricular fibrillation (VF), usually lacking an organized reentry, are rarely interrupted by pacing.

ICDs allow delivering different ATP therapy types, in particular the two most important are: (1) burst with impulse trains at constant coupling in a programmable number; and (2) ramp with autodecremental coupling (Figure 1).

WHEN SHOULD WE PROGRAM ATP?

Schaumann *et al.*^[12], in 1998, evaluated whether ATP could be safely used even in those patients in whom ATP testing on induced VT was not performed. All devices were programmed with the same ATP scheme in the VT zone (< 200 bpm): 3 ramps from 8 to 10 impulses, with 8 ms decrease and 81% coupling. The study enrolled 200 patients divided in two groups: The first included subjects in whom efficacy of ATP was demonstrated on sustained VT induced in the electrophysiology laboratory (Tested group); in the second group ATP was programmed empirically (Empirical group). During the follow-up period (20 ± 11 mo) ATP therapy proved to be highly effective in both groups. In particular, success rate was 95% in the T group and 90% of the E group. Moreover, this study provided a strong response to one of the most frequent criticism to pacing therapy, the risk of tachycardia acceleration. Acceleration after ATP occurred only in 2% in group T and 5% in group E. The conclusions of the study were, therefore, that the success rate of ATP therapy was not dependent on efficacy testing and ATP was recommended for VT

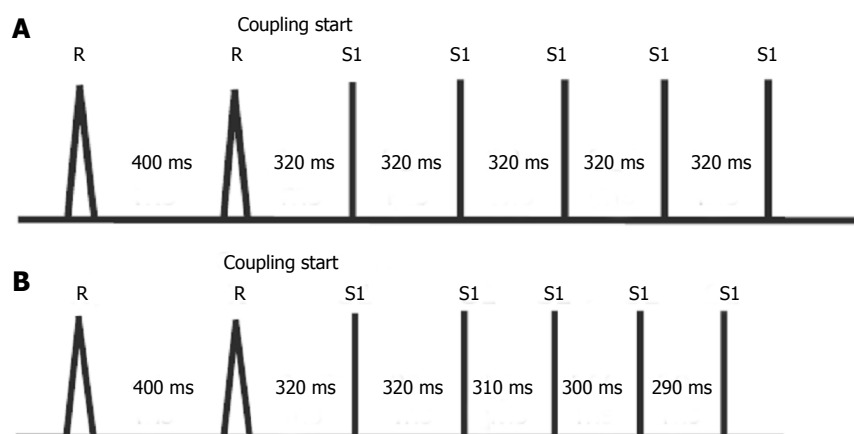


Figure 1 Examples of antitachycardia pacing patterns. A: Burst with 5 impulses and coupling at 80%; B: Ramp with 5 impulses, coupling at 80% and with a 10 ms decrease.

treatment in any patient with ICD.

During the 90s other studies were published about the efficacy and the safety of the ATP therapy. These studies reported that ATP sequences successfully interrupted 78%-94% of slow VT (< 188 bpm), with an acceleration rate between 2% and 4%^[13-15]. Based on these results the ATP was conventionally programmed only for slower VT, presumably hemodynamically well tolerated.

Fast VTs (from 188 to 250 bpm) were, instead, still treated like VF, with high energy shocks. Faster VTs have a shorter excitable gap that is more difficult to be penetrated and interrupted by a pacing stimulus.

Nevertheless, in 2001, Wathen *et al.*^[16] with the PainFREE Rx I trial showed, for the first time, that ATP therapy was also effective for fast VT (FVT). This trial, however, had many limitations: Only patients with coronary artery disease were included; it was nonrandomized; ICDs were programmed with a short detection interval (12 of 16 beats), which could imply that many treated arrhythmias were non-sustained VTs, destined to run out on their own.

In 2004, the same authors published a prospective, single-blinded trial, the PainFREE Rx II^[17], which exceeded the limits of the first study. This trial enrolled 637 ICD patients randomized to ATP ($n = 315$) or shock therapy ($n = 322$) to evaluate episode duration between the two arms (primary endpoint). Baseline clinical variables were similar between the 2 groups, in particular age (average, 67 years), ejection fraction (average, 32%), sex (male 77%), coronary artery disease (85%), syncope (35%). Both groups received similar pharmacological therapies. Primary prevention indication for ICD involved 44% of patients. Fast VT was defined as a zone between 240 and 320 ms (188-250 bpm); faster rates were considered as VF. In the first group the initial therapy in the FVT zone was ATP (8 impulses burst at 88% of arrhythmia cycle length), while in the second group shock was directly delivered at the defibrillation threshold (DFT) + 10 J. The detection for FVT, as well as for VF, was 18 of 24 beats. The

first important result was that the FVTs represented 76% of all ventricular arrhythmias. In the ATP group the bursts resulted effective in 77% of the FVTs; when it failed, shocks were effectively delivered to interrupt the arrhythmia. There was no significant difference between percentage (and number) of patients who had fast VT in either the ATP or shock arms (15% vs 16% respectively). In addition, after accounting for 2 patients in the ATP arm who together had 131 episodes, numbers of fast VT in the ATP and shock arms were similar (151 vs 144, respectively). Moreover, there was no significant difference in episode duration between the shock and ATP arms (10 s vs 9.7 s, respectively). Not all patients with fast VT episodes received shock therapy in the shock arm (only 67% of episodes being shocked) and 30% of fast VT episodes self-terminated after detection. In comparison, only 20% of patients in the ATP arm received shocks. The acceleration was rare, with 2% incidence in the ATP arm and 1% the shock arm. Syncopal events were also low and comparable between the two groups. It is interesting to note that the success rate of the first shock (92%) was identical in both groups, even if delivered after an ineffective ATP. In conclusion, this study showed that ATP therapy was safe and effective compared to shocks also for the treatment of FVT, with a 70% relative reduction of shocks in the ATP group.

After these studies, scientific community started to consider ICDs as stimulation devices with a defibrillation backup, only as a security option, with a consequent improvement in patient's quality of life. It is noteworthy that these trials used bursts coupled to 88% of arrhythmia cycle: This was a "little aggressive" therapy, so the risk of arrhythmias acceleration was low^[18].

In order to avoid significant delays in the delivery of shock therapy (in case of ATP failure) algorithms of ATP sequences during or before capacitor charging were soon implemented in the VF zone for most manufacturers; this strategy has been subsequently clinically validated as safe and effective^[11].

WHICH PATTERN OF ATP SHOULD BE PREFERRED?

The importance of the ATP therapy in the context of ICD programming is well documented, but we should understand if there is a specific pacing pattern to prefer, especially in relation to the type of ventricular arrhythmia.

Several studies comparing the efficacy of two different types of ATP pattern (burst and ramp) on induced VTs did not show significant differences in the percentage of success: Gills *et al.*^[19] reported 76% efficacy for burst and 68% for ramp in a study with 21 patients enrolled; Calkins *et al.*^[20] reported a success rate of 70% for burst and 72% for ramp (44 patients); Kantoch *et al.*^[21] reported a 69% success for burst and 72% for ramp in 31 patients. The rate of acceleration was low and did not change significantly between the two patterns.

Burst vs Ramp were evaluated also in the setting of spontaneous VTs: Gills *et al.*^[19] found, in this case, a success rate of 96% for burst and 93% for ramp; Ardashev *et al.*^[22] reported 61% efficacy for burst and 76% for ramp with 54 patients enrolled. The latter study, therefore, was the only indicating a significant difference in efficacy between the two techniques ($P < 0.01$), in favor of the ramp.

Overall, from the analysis of several studies, there was not a clear difference in the efficacy of burst and ramp for treatment of non-FVT, in ischemic and non-ischemic cardiomyopathies. The choice of the pattern was, therefore, left to the clinician's experience and to an empirical case-by-case approach^[18]. An important exception is represented by patients with arrhythmogenic right ventricular dysplasia: The success rate of ramp fell down to 25%, with an acceleration rate of 24%, while the burst resulted in a better outcome^[22].

Different considerations have to be made for FVT in which burst seems to be better. The PITAGORA ICD^[23] trial was a randomized Italian study that aimed to compare two ATP strategies (burst and ramp) in terms of efficacy, arrhythmia acceleration and syncope on FVT episodes. Two hundred and six patients were randomized into two groups, with two different therapies: 88% coupling-8 impulses burst vs 91% coupling-8 impulses ramp with 10 ms decrement. The FVT zone was programmed between 188 and 250 bpm, with a detection of 18 of 24 beats. The study demonstrated that burst was significantly more effective than ramp (75% vs 54%; $P = 0.015$) to interrupt FVT episodes. Regarding safety, burst was associated with a lower percentage of acceleration compared to ramp (2% vs 7%), although this difference was not statistically significant. The overall incidence of syncope was 1%. The adopted strategy, with ATP as the first therapy and prolonged detections (18 of 24 compared to 12 of 16), allowed the end of the arrhythmic episode before shock delivery in 81% of the cases^[23].

In 2010, the results of the trial ADVANCED-D^[24] were

published. This study aimed to compare 8 impulses burst with 15 impulses burst on FVT. Nine hundred and twenty-five patients were enrolled and randomized into two groups treated with the two different sequences of ATP. The window of FVT remained between 188 and 250 bpm and detection 18 of 24 beats. No significant difference was detected between the two sequences, 8 pulses burst terminated 64% of episodes compared to 70% of 15 pulses burst. Moreover, there were not significant differences also regarding syncope or rate of acceleration. The sequence of 15 pulses was more effective only in patients with no history of HF ($P = 0.014$) and with left ventricular ejection fraction $> 40\%$ ($P = 0.016$). The conclusion of the study was that an ATP sequence of 15 pulses can be considered effective, but also safe, in FVT comparable with a sequence of 8 pulses.

ATP IN BIVENTRICULAR ICD

Thanks to the coronary sinus lead which stimulates the left ventricle, cardiac resynchronization therapy devices equipped with a cardioverter defibrillator (CRTD) offer the potential for alternative sites for ATP. The possibility to deliver therapy from either the left ventricular lead (LV-ATP) or the left and the right ones simultaneously (BiV-ATP) may theoretically increase the rate of success compared to right ventricular stimulation (RV-ATP). Several studies reported an increased efficacy of BiV-ATP configuration compared to the RV-ATP for termination of VT events both slow and fast^[25]. However, the ADVANCED CRT-D^[26] trial demonstrated a significant superiority of BiV-ATP only in ischemic patients with FVTs. Moreover, few papers compared LV-ATP with the other configurations. In this context, a study by Haghjoo *et al.*^[27] compared efficacy and safety of the three ATP therapy sites (RV, LV and BiV) for VT treatment in patients with a CRTD device. The study enrolled 89 patients (with ischemic and non-ischemic etiologies) divided into 3 groups with 3 different pacing sites during ATP. The mean follow-up was 38 mo with 259 detected VT episodes in 46 patients. The results showed: (1) greater efficacy of BiV-ATP compared to both LV-ATP and RV-ATP for the treatment of FVT (188-250 bpm); (2) higher success rate and lower acceleration rate of both LV-ATP and BiV-ATP compared to RV-ATP for slower VTs (< 188 bpm)^[27]. Therefore, left ventricular lead allows further possibilities to increase the success of ATP; in patients with CRTD it is recommended to set either biventricular or left ventricular ATP therapy for the slowest therapy zone (< 188 bpm), while biventricular ATP should be programmed for faster arrhythmias.

THE STANDARDIZATION OF THE ICD PROGRAMMING

The therapeutic programming of an ICD involves several

parameters. It is worthwhile to understand if a strategic standardized choice can be as effective and safe as a patient-tailored programming, which is inevitably time-consuming for the physician. Indeed, the customization of the ICD setting is useful only if it provides improvements in clinical outcomes or in patient's quality of life; otherwise both the simplification and the standardization of the therapy can be convenient and minimize the risk of random errors.

In this framework, EMPIRIC trial^[10] randomized 900 patients with ICDs (48% implanted for primary prevention, 52% for secondary prevention) to a standardized (EMPIRIC group) or a physician-tailored (TAILORED group) VT/VF programming and followed them for 1 year. The EMPIRIC programming (Table 1) was created by taking into account some key strategies to safely reduce the number of shocks for VT/VF and supraventricular tachycardias (SVTs) and to avoid untreated slow VT: (1) three attempts of ATP for VT < 200 bpm. In particular, 2 burst of 8 intervals coupled at 88% with 20 ms decrement and 1 ramp of 8 intervals coupled at the 81% with 10 ms decrement; (2) a sequence of ATP for FVT between 200 bpm and 250 bpm. In particular, 1 burst of 8 intervals coupled at the 88% (as in the PainFREE Rx II); (3) long detection time (18 out of 24) in VF and FVT (as in the PainFREE Rx II, PITAGORA ICD e ADVANCED-D trials); (4) first shock at the maximum energy in VF and FVT zones to reduce the risk of multiple shocks; and (5) discrimination criteria for SVT in the VF zone.

The results of the study reported no significant differences in the number of deaths, syncope events and arrhythmias acceleration between the two groups of patients. Moreover, the rate of hospitalization was significantly lower ($P = 0.001$) in the EMPIRIC group^[10]. The overall ATP efficacy was 92%; consequently, a significant reduction of VT shocks was reported in the EMPIRIC group compared to the TAILORED group ($P < 0.001$). It is interesting to observe that the EMPIRIC group had a threshold for the VT zone of 150 bpm, value which is lower than the average in the TAILORED group (171 bpm). Nevertheless, the study did not show an increase of the SVTs inappropriately treated, thanks to the discrimination algorithms. To conclude, EMPIRIC study entails that a simplified and standardized programming is possible, without reducing efficacy and safety of the therapy.

The PREPARE study^[1] analyzed a different standardized setting with the aim of reducing shocks occurrence, syncopes and untreated symptomatic VT in patients with ICDs for primary prevention^[28]. The PREPARE programming was developed on the basis of some key strategies: (1) to detect only fast tachycardias (> 182 bpm); (2) to discriminate only sustained tachycardias (discrimination set to 30 of 40 in the FVT and FV zones); (3) to deliver ATP as the first therapy for FVT; (4) to always deliver the high-energy shock (at least 30 J); and (5) to use discrimination criteria for SVT up to 200 bpm.

The PREPARE programming (Table 2) provided a lower mortality ($P = 0.01$) compared to a control cohort of patients from the EMPIRIC^[10] the MIRACLE ICD (Multicenter InSync Implantable Cardioverter Defibrillators Trial) studies. The extension of the detection duration (30 out of 40 beats), fast rate cutoffs for the therapy (182 bpm), the use of SVT discrimination criteria reduced the number of shocked episodes. Moreover, at 12 mo follow up the incidence of syncopal events was 1.6% and mortality 4.9%. This study demonstrated how a strategically chosen tachycardia detection and conservative therapy options, can make the device more acceptable by the patient without negatively affecting its efficacy and safety.

In 2012 a large randomized multicenter study, Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy (MADIT-RIT)^[29], was published in the New England Journal of Medicine. The aim of this study was to test two ICD programming strategies in patients with an ICD implanted for primary prevention. In particular, the first strategy was characterized by therapies only for high heart rates (> 200 bpm) while the second was to increase of the detection delay duration before the initiation of therapies, with values variable in relation to the heart rate (60 s delay for rates between 170 bpm and 199 bpm, 12 s delay for rates between 200 bpm and 249 bpm, 2.5 s delays for higher rates). As explained by the authors, the MADIT-RIT study was based on the hypothesis that these two strategies would have reduced the number of patients receiving appropriate and inappropriate shocks and ATPs, compared to a conventional programming, without increasing mortality and morbidity. The study involved 98 centers in the United States, Canada, Europe, Israel and Japan, enrolling a total of 1500 patients with either ischemic or non-ischemic heart disease and indicated for implantation of an ICD or a CRTD in primary prevention. Patients with atrial fibrillation were excluded. The first episode of inappropriate therapy represented the primary endpoint of the study: This outcome was evaluated by comparing each treatment group with the control group. The rates of both syncope and mortality (for any cause) were secondary endpoints. A significant reduction in the risk of any inappropriate therapy was observed in the two groups with "unconventional" programming in a follow-up of 1.4 years: The results showed a 79% relative risk reduction for patients with "High-Rate Therapy" and a 76% risk reduction for those with "Delayed Therapy" (HR of "High-Rate therapy" vs conventional therapy: 0.21, 95%CI, $P < 0.001$; HR of "Delayed Therapy" vs conventional therapy: 0.24, 95%CI, $P < 0.001$). Another significant result of the MADIT-RIT regarded one of the secondary endpoints of the study. The "High-Rate Therapy" programming reduced the risk of death from any cause (HR = 0.45, $P = 0.01$) by a factor of 55% compared to conventional therapy. The group with "Delayed Therapy" showed a 44% reduction of the mortality risk, but it did not reach statistical significance compared to the conventional therapy group (HR = 0.56,

Table 1 EMPRIC programming

Detection	Threshold (bpm)	Beats to detect	Therapies
VF	250	18 out of 24	30 J × 6
FVT	200	18 out of 24	1 × burst, 30 J × 5
VT	150	16	2 × burst, 1 × ramp, 30 J × 3

Burst: 8 impulses coupled at the 88% with 20 ms decrement; Ramp: 8 intervals coupled at the 81% with 10 ms decrement. VF: Ventricular fibrillation; FVT: Fast ventricular tachycardia; VT: Ventricular tachycardia.

$P = 0.06$). Concerning syncopal episodes, no difference among the three groups was observed.

Recently, the OBSERVational registry on long-term outcome of ICD patients^[30] confirmed, in a “real world setting”, the results of MADIT-RIT trial. OBSERVO-ICD was a multicenter, retrospective, registry enrolling (from 2010 to 2012) all consecutive patients undergoing ICD implantation in 5 Italian centers. The aim of the study was to test whether a too aggressive ICD programming could be associated with electrical storms (ES). A total of 1319 patients were enrolled, both primary and secondary prevention. During follow up (median 39 mo) 4.7% of patients experienced at least 1 ES episode. Patients with ES presented with significantly lower VF detection zone ($P = 0.002$), more frequently had ATP therapies during capacitor charging programmed off ($P = 0.001$), and less frequently had delayed therapies for VT zone ($P = 0.042$) and VF zone ($P = 0.036$). Patients with ES had a significantly higher incidence of death and HF-related death compared to patients with no VTs and patients with unclustered VTs/VFs ($P = 0.025$ and $P = 0.001$, respectively). In conclusion, patients with less aggressive ICD programming (higher VF detection rates, higher detection times, ATP therapies during capacitor charging turned on) had a decreased likelihood of ES and lower risk of death.

CONCLUSIONS AND “TAKE HOME MESSAGES”

ATP is a safe, effective and painless therapy for VTs with large clinical evidence supporting its routine use in primary and secondary ICD patients^[31,32].

ATP therapy is effective in interrupting VTs, both slow and fast, with a consequent reduction of unnecessary shocks and an improvement of clinical outcome, patients' quality of life and device longevity^[12,16,17,31].

In a recent expert consensus document on ICD programming, from the most important world leading arrhythmological societies^[32], it was stated that “in all patients with structural heart disease... that ATP therapy be active for all ventricular tachyarrhythmia detection zones to include arrhythmias up to 230 bpm, to reduce total shocks except when ATP is documented to be ineffective or proarrhythmic”.

In patient with inherited cardiac channelopathies

Table 2 PREPARE programming

Detection	Threshold (bpm)	Beats to detect	Therapies
VF	250	18 out of 24	30 J/35 J × 6
FVT	182	18 out of 24	1 × Burst, 30 J/35 J × 6
VT	167	32	Off

Burst: 8 impulses coupled at the 88%. VF: Ventricular fibrillation; FVT: Fast ventricular tachycardia; VT: Ventricular tachycardia.

(Brugada syndrome, Long and Short QT syndrome, catecholaminergic polymorphic VT, early repolarization syndromes) the index clinical arrhythmia is polymorphic VT or VF: These arrhythmias usually lack an organized reentry and are rarely interrupted by pacing, so ATP should not be routinely programmed^[31,32].

As concerns the type of ATP to be used, clear conclusions cannot be drawn, except for the treatment of fast TV (188 bpm–250 bpm) for which greater efficacy and safety of burst was showed compared to ramp^[23,31,32]. So, as a first choice, it is indicated to program burst in preference to ramp. Ramp should be reserved for patients in whom burst fails and ramp is proven to be effective. A “little aggressive” burst programming (several studies used impulses coupled at the 88%) seems to be related to lower rates of arrhythmia acceleration^[18]. Moreover, the optimal number of impulses in each sequence of ATP has been proved to be minimum 8^[24,32].

In patients with biventricular devices the lead placed in the coronary sinus offers further opportunities for a successful ATP therapy, due to biventricular pacing (ATP-BiV) or left ventricular only pacing (LV-ATP)^[25-27].

In the last years, a great effort has been devoted to standardize the ICD programming, particularly in the primary prevention. Two studies provided excellent results in this field: EMPERIC^[10] and PREPARE^[11]. The fundamental principles of these programming strategies were: (1) prolonged detection for the VF zone (18 out of 24 and 30 out of 40); (2) delayed detection time in any window; (3) SVT discrimination criteria up to 200 bpm; (4) ATP as first therapy for FVT; and (5) first shock at maximum energy in the VF zone to reduce the risk of multiple shocks.

The MADIT-RIT^[29] trial and the OBSERVO-ICD registry^[30] have recently confirmed this programming philosophy, showing that higher cut-off rates, more prolonged detections and ATP during capacitor charging reduce the number of inappropriate and unnecessary therapies compared to a more “conventional” programming. This reduction translates in a better clinical outcome in terms of morbidity and even mortality. The results of these studies add new chapters in the development of the ICD therapy, especially in primary prevention patients.

More studies are needed, instead, in a secondary prevention setting to design effective ATP strategies. Secondary prevention patients can represent an

opportunity to a more “tailored” approach compared to primary prevention, on the basis of the knowledge of arrhythmia history (ECG morphology, cycle length, arrhythmia mechanism, patient’s tolerance, hemodynamic impact)^[31]. In patients with prior known VTs the device must be programmed to cover all clinical arrhythmias; slower monomorphic and better tolerated VTs should be treated with at least 2-3 sequences of ATP and at least 8 impulses. A second burst of ATP increases efficacy from 64% to 83% in FVT range, although programming > 2 bursts usually does not add further benefit^[31,32].

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Retrospective Cohort Study

Clinical characteristics and outcomes of octogenarians presenting with ST elevation myocardial infarction in the Australian population

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Abstract

AIM

To investigate the characteristics and outcomes of octogenarians who presented with ST-elevation myocardial infarction (STEMI) compared to non-octogenarians and to investigate the outcomes of octogenarians that received primary percutaneous coronary intervention (PCI) compared to those managed conservatively.

METHODS

We performed a single center retrospective case controlled study. All octogenarians who presented with STEMI to a tertiary referring hospital between 2007 and 2012 were included. The subsequent non-octogenarian patient who presented with a STEMI following the octogenarian patient was assigned to the control group in a 1:1 manner. The outcomes measured were peri-procedural cardiac arrest, death on table, cerebrovascular accidents (CVA), in-hospital and 30-d mortality.

RESULTS

A total of 146 patients were analyzed. The octogenarian group had a higher percentage of females, higher overall comorbidities, higher Charlson Comorbidity Index score, worse renal function and were more likely to require residential care and home help. The octogenarian group were also less likely to have PCI attempted and had a longer symptom onset to PCI

time. Mortality rate was high amongst octogenarians who presented with STEMI. However, those managed conservatively had a higher in-hospital and 30-d mortality rate

CONCLUSION

Octogenarians who presented with STEMI that were managed conservatively had a higher mortality rate compared to those who had primary PCI. Therefore, we propose that revascularization may be beneficial to patients in this age group.

Key words: Coronary disease; Acute coronary syndrome; Myocardial infarction; Percutaneous coronary intervention; Aged 80 and over

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Core tip: The octogenarian group represents a complex population with multiple comorbidities. Percutaneous coronary intervention in this group is challenging and is associated with a high rate of failure and complications. This study shows that the mortality rate amongst octogenarians presenting with ST elevation myocardial infarction is high. However, there may be a mortality benefit in those treated with percutaneous coronary intervention, compared to those managed conservatively.

Sim WL, Mutha V, Ul-Haq MA, Sasongko V, Van-Gaal W. Clinical characteristics and outcomes of octogenarians presenting with ST elevation myocardial infarction in the Australian population. *World J Cardiol* 2017; 9(5): 437-441 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i5/437.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i5.437>

INTRODUCTION

Advanced age is associated with increased risk of acute coronary syndrome (ACS) and cardiovascular comorbidities^[1]. The octogenarian population (age \geq 80 years) is a fast growing segment of the population worldwide, and represent a high risk group for procedural complications during percutaneous coronary intervention (PCI) particularly in the settings of ST-segment elevation myocardial infarction (STEMI)^[2]. These patients are underrepresented in randomized clinical trials evaluating primary PCI for STEMI and a high mortality has been reported^[3,4]. These patients are typically treated less aggressively than are younger patients, due partly to the increased risk of adverse events and PCI related complications, and partly to a lack of standard management guidelines. Evidence based management of octogenarian patients with STEMI thus remains suboptimal despite the high mortality^[2]. The overseas observational trials have suggested that despite the recommendations being

that age should not influence the decision of reperfusion strategy in STEMI patients, older age remains one of the strong predictors of not receiving it. There is paucity of Australia data on outcomes of octogenarian who present with STEMI. In this context, the aim of our study was to assess the clinical characteristics and outcomes of octogenarians presenting with STEMI, as compared with non-octogenarian patients (age < 80 years), as well as the outcomes of octogenarians who received primary PCI, compared to those that were managed conservatively.

MATERIALS AND METHODS

This study is a single center retrospective case controlled study including all octogenarians who presented with STEMI between 2007 and 2012 in a tertiary Australian hospital. The subsequent non-octogenarian patient who presented with STEMI following an octogenarian STEMI was assigned to the control group in 1:1 manner. Detailed data on baseline and procedural characteristics and patient comorbidities were obtained through electronic medical records, and compared between octogenarian and non-octogenarian STEMI patients. The charlson comorbidity index (CCI) was calculated based on the patient's comorbidities. CCI predicts long-term survival according to a patient's medical condition^[5]. STEMI was defined as persistent angina for 20 min in conjunction with either: (1) an ST-segment elevation at the J point of 0.25 mV in men aged < 40 years or 0.2 mV in men aged > 40 years or 0.15 mV in women in the precordial leads V2 to V3, and 0.1 mV in all other leads; or (2) the presence of a new left bundle branch block^[6]. PCI success was defined as TIMI 2 or 3 flow post intervention. Left ventricular ejection fraction (EF) was derived either from the echocardiogram performed following the presentation or coronary angiogram during the index admission. Outcomes compared between the two groups included peri-procedural cardiac arrest, death on table, cerebrovascular accident (CVA), in-hospital and 30-d mortality. CVA was defined a clinical evidence of neurological deficit leading to a documented diagnosis of transient ischaemic attack or stroke. Subgroups of octogenarian STEMI patients who received PCI vs who did not (conservatively managed) were also compared for baseline and clinical characteristics. In-hospital and 30-d mortality was compared between all subgroups and independent predictors calculated.

All data were analyzed using IBM SPSS v22 and presented as percentages or mean value \pm standard deviation (SD). Independent *t* test was used to compare continuous while χ^2 and Fisher's exact tests were performed for categorical data. Logistic regression and multivariate analysis were performed to identify independent predictors. A two tailed *P* value of < 0.05 was considered statistically significant. The statistical methods of this study were reviewed by our biostatistics expert Dr. Asrar Ul-Haq, MBBS.

Table 1 Baseline characteristics, procedural data, and outcomes of octogenarians as compared to non-octogenarians (controls)

	Octogenarians (<i>n</i> = 73)	Controls (<i>n</i> = 73)	<i>P</i>
Age	85.2 ± 4.1	67.1 ± 5.3	< 0.005
Females	56	29	< 0.005
Residential care	23	2.7	< 0.005
LLC	11	0	< 0.005
HLC	12	2.7	< 0.005
Home help	25	0	< 0.005
Medical comorbidities			
Diabetes	38	19	< 0.05
eGFR	48.7 ± 19.9	68.1 ± 20.3	< 0.005
PVD	30	12	< 0.05
Prior IHD	36	20	0.06
EF	53.6 ± 14.1	50.8 ± 13.1	0.4
Charlsons	3.2 ± 2.3	1.7 ± 2.2	< 0.005
Presentation and procedural characteristics			
Location of MI			
Anterior	51	49	0.8
Inferior	42	47	0.5
Lateral	4.1	4.1	1.0
PCI attempt	47	84	< 0.005
PCI success (TIMI 2-3)	91	99	0.1
Symptoms onset to PCI < 6 h	16	45	< 0.005
Outcomes			
Peri-procedural cardiac arrest	5	3	0.1
Death on table	1.8	0.9	0.2
Stroke	1.4	0	0.3
Inhospital mortality	28	7	< 0.005
30-d mortality	45	12	< 0.005

Data are means ± SD or *n* (%). LLC: Low level care; HLC: High level care; PVD: Peripheral vascular disease; EF: Ejection fraction; PCI: Percutaneous coronary intervention; MI: Myocardial infarction.

RESULTS

Octogenarians vs non-octogenarians

A total of 146 patients were analysed (octogenarians = 73; non-octogenarians = 73). The mean age was 85.2 ± 4.1 years in the octogenarian group and 67.1 ± 5.3 years in the control group (Table 1). The octogenarian group had a higher percentage of females (56% vs 29%, *P* < 0.005), higher overall comorbidities, a higher CCI score (3.2 ± 2.3 vs 1.7 ± 2.2, *P* < 0.001), were more likely to require residential care (23% vs 2.7%, *P* < 0.001) as well as home help (25% vs 0%, *P* < 0.001), and had worse renal function (eGFR 48.7 ± 19.9 vs 68.1 ± 20.3 mL/min per 1.73 m², *P* < 0.001).

Octogenarians were less likely to have PCI attempted compared to the non-octogenarians (47% vs 84%, *P* < 0.001). The rate of symptom onset-to-PCI of < 6 h was significantly lower in octogenarians (16% vs 45%, *P* < 0.001). The rate of PCI success was high in both groups (91% vs 99%, *P* = 0.1). Reasons PCI was not attempted in non-octogenarians include: No culprit found (3), embolic event (1), recent CVA (1), known or new triple vessel disease/complex anatomy (2), other comorbidities (5); and in octogenarians: No culprit found (9), embolic event (2), recent CVA (4), known or

Table 2 Baseline characteristics and outcomes of octogenarians who received percutaneous coronary intervention compared to conservatively managed octogenarians (no-percutaneous coronary intervention)

	PCI (<i>n</i> = 34)	No-PCI (<i>n</i> = 39)	<i>P</i>
Age	84 ± 3.4	86 ± 4.3	< 0.05
Females	44	67	0.06
Residential care	3	41	< 0.005
LLC	3	18	< 0.005
HLC	0	23	< 0.005
Home help	18	35	0.2
Medical comorbidities			
Diabetes	32	44	0.3
eGFR	54 ± 23	44 ± 16	< 0.05
PVD	21	38	0.1
Prior IHD	35	36	1
EF	54 ± 13	53 ± 16	0.2
Charlsons	2.52 ± 2	3.8 ± 2	< 0.05
Presentation			
Location of MI			
Anterior	41	59	0.2
Inferior	50	36	0.2
Lateral	6	3	0.6
Outcomes			
Inhospital mortality	18	37	0.1
30-d mortality	29	59	< 0.05

Data are means ± SD or *n* (%). LLC: Low level care; HLC: High level care; PVD: Peripheral vascular disease; EF: Ejection fraction; PCI: Percutaneous coronary intervention; MI: Myocardial infarction.

new triple vessel disease/complex anatomy (13), other comorbidities (11). Octogenarians had a significantly higher overall in-hospital mortality (28% vs 7%, *P* < 0.005) and 30-d mortality (45% vs 12%, *P* < 0.001).

The independent predictors of 30-d mortality in octogenarians included age (OR 1.20/year of advancing age, *P* < 0.01), place of residence (OR = 4.4, *P* < 0.01 for nursing home), conservative management (No intervention - OR 2.77, *P* < 0.05), and declining renal function (OR = 0.9, *P* < 0.05).

PCI vs conservatively managed octogenarians

The 39 (53%) octogenarians who did not receive PCI were older (86 ± 4.3 years vs 84 ± 3.4 years, *P* < 0.05) and were more likely to be in residential care (41% vs 3%, *P* < 0.001), had higher CCI score (3.8 ± 2 vs 2.52 ± 2, *P* < 0.05) and worse renal function (eGFR 44 ± 16 mL/min vs 54 ± 23 mL/min per 1.73 m²). Type of myocardial infarction was not different as compared to octogenarians who received PCI (Table 2).

Mortality rate was high among octogenarians who presented with STEMI. However, those who were managed conservatively had a higher in-hospital and 30-d mortality (37% vs 18%, *P* = 0.1; and 59% vs 29%, *P* < 0.05 respectively).

Independent predictors of intervention in octogenarians included younger age (OR = 0.86, *P* < 0.05), place of residence (OR = 0.1, *P* < 0.05 for nursing home), lower CCI (OR = 0.7, *P* < 0.05), and renal

function (OR = 1.03, $P < 0.05$).

DISCUSSION

High mortality

Our study demonstrated that mortality rate amongst octogenarians presenting with STEMI is high in Australian population despite the offered treatment, although much worse when treated conservatively. This appears to be associated with higher overall comorbidities, higher CCI score, worse renal function, and need for residential care or home help (which maybe the indirect measure of overall comorbidities and physical state). These findings are consistent with overseas studies looking at similar age groups^[7-9]. Some factors reported to affect the mortality in these studies include heart failure, multiple co-morbidities, cachexia, cognitive state, history of intra-cranial bleeding and pre-hospital physical activity status^[10,11]. Furthermore, it has been shown that the elderly are less likely to receive evidence based medical treatment such as aspirin, clopidogrel, beta-blockers, statins or glycoprotein IIb/IIIa inhibitors^[7,8]. This may be due to concerns with regards to potential side effects in this age group. Previous studies have also shown that the elderly is associated with a higher rate of PCI failure. However, this is not reflected in our study, likely because the candidates for treatment were carefully selected.

Underuse of invasive treatment

Our study suggested that despite having a higher mortality rate, octogenarians are less likely to have PCI attempted as compared to non-octogenarians. Frailty, co-morbidities and time delays have been shown to contribute to the underuse of invasive therapies. In our study, the proportion of those who received PCI in less than 6 h was significantly lower in the octogenarian group. This might reflect difficulty in decision-making with regards to reperfusion strategy. Atypical clinical presentation is also more common in the elderly and could contribute to time delay as well as the higher prevalence of cardiac failure. In addition, female gender was more prevalent in the octogenarian group. Previous studies have shown that female gender is associated with lower use of invasive therapies, especially in the elderly^[12].

Invasive treatment appears beneficial

Another major finding of our study is that despite a relatively poor prognosis, octogenarians who received primary PCI had a significantly lower 30-d mortality. This however maybe related to the selection bias, a limitation of observational study design. Patients managed conservatively in our study were older, more likely to be in residential care, had a higher CCI score and worse renal function, and this represents a group with higher risk profile. The most common reasons PCI was not performed in the elderly were triple vessel disease/complex anatomy, other co-

existing comorbidities and the absence of a clear culprit lesion. There was no significant difference in in-hospital mortality between those managed who received intervention and those managed conservatively. Other factors affecting 30-d mortality included age, place of residence and declining renal function, highlighting the complexity of this patient population.

Limitations

Our study is not randomized, and therefore limited by selection bias. However, it is an "all comers" registry which reflects "real world" data on management and outcomes of elderly patients who presents with STEMI. A randomised trial in this particular group is not viable. Propensity score matching would be the next best option and requires larger studies. Furthermore, we did not evaluate long term mortality and re-infarction rates, which may provide incremental information and a better picture of the utility of invasive management in this group.

In conclusion, this study is the first Australian report on the outcomes of octogenarians who present with ST-elevation myocardial infarction. This group represents a complex population with multiple medical comorbidities and PCI is challenging, associated with high failure and complication rates. Consequently, mortality is high in this group. However, the detrimental prognosis of conservatively managed octogenarians and relative mortality benefit associated with PCI suggests that revascularization therapy may benefit this age group.

COMMENTS

Background

The elderly have an increased risk of acute coronary syndrome. However, there are more likely to be managed conservatively compared to the younger cohort. This is due to concerns regarding procedural complications and success. The elderly is also under-represented in major clinical trials evaluating primary percutaneous coronary intervention (PCI). Recognizing this there have been recent overseas studies evaluating the elderly and primary PCI.

Research frontiers

This study is the first to evaluate the characteristics and outcome of octogenarians who presents with ST-elevation myocardial infarction (STEMI) in an Australian setting. The authors also evaluated the outcomes of octogenarians who received primary PCI compared to those that were managed conservatively.

Innovations and breakthroughs

This paper showed that despite poor prognosis among octogenarians who presents with STEMI, primary PCI may offer some benefit, with significantly lower 30 d mortality in the group that received it.

Applications

Primary PCI should be considered in octogenarians who presents with STEMI. The patient's co-morbidities, quality of life and life expectancy should be taken into account when making this decision.

Terminology

Primary PCI consists of urgent balloon angioplasty (with or without stenting), without the previous administration of fibrinolytic therapy or platelet glycoprotein IIb/IIIa inhibitors, to open the infarct-related artery during an acute myocardial infarction with ST-segment elevation.

Peer-review

This is an interesting and well-written article dealing with care on octogenarians after acute myocardial infarction. The authors have found worse clinical characteristics in octogenarians in comparison with non octogenarians, as well as lower referral for interventional procedures.

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Retrospective Study

Jailing polymer jacketed guide-wires during bifurcation coronary interventions is associated with procedural myocardial infarction

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Abstract

AIM

To study the relationship of jailed polymer jacketed guide wires (PGW) with procedural myocardial infarction (PMI) after bifurcation coronary interventions.

METHODS

Consecutive bifurcation interventions performed from January 2010 to October 2014 were included in the study. Chart review was performed to obtain demographic, clinical and procedural data. PMI was defined as Creatine Kinase MB > 3 × upper reference limit of normal. Multivariate logistic regression was used to ascertain relationship of PGW use with PMI.

RESULTS

Two hundred and ninety-three patients (age 63.5 ± 12.3 years; 33.8% diabetic) were included in the study. Eighty point two percent ($n = 235$) were true bifurcation lesions use of PGW was associated with PMI on univariate analysis (OR = 4.1; $P = 0.002$). This association remained significant after adjusting for other possible risk factors (OR = 3.5; $P = 0.02$).

CONCLUSION

Our results suggest that PGW use for side branch protection may be associated with PMI. Randomized studies are needed to validate these findings.

Key words: Coronary bifurcation lesions; Percutaneous coronary intervention; Procedural myocardial infarction; Jailed guidewire; Polymer shearing

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Core tip: This is a retrospective study aiming to investigate the relationship of jailed polymer jacketed guide wires (PGW) with procedural myocardial infarction (PMI) after a bifurcation coronary intervention. There is concern that this causes polymer shearing and distal micro-embolization. Our data suggests that jailed PGW are strongly associated with PMI, even after adjusting for pertinent risk factors. Thus caution should be exercised in routinely jailing PGW until further definitive data are available.

Chatterjee A, White JS, Hashim T, Leeser MA. Jailing polymer jacketed guide-wires during bifurcation coronary interventions is associated with procedural myocardial infarction. *World J Cardiol* 2017; 9(5): 442-447 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i5/442.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i5.442>

INTRODUCTION

Coronary bifurcation lesions (CBL) are a challenging subset of day to day coronary interventions with a higher adverse event profile as compared to non-bifurcation lesions^[1]. In the past decade, multiple studies have investigated the optimum approach to bifurcation lesions vis-à-vis simple (provisional side branch stenting only) vs complex (mandatory main and side branch stenting) approaches^[2-4]. These have led to a widespread consensus that the simple approach should be preferred in majority of CBLs as the complex strategy showed higher incidence of adverse cardiac events, mainly myocardial infarction^[5].

In the simple approach, a coronary guidewire is frequently inserted into the side-branch (SB) as a strategy to prevent occlusion. This is considered to be an important step as side branch compromise is associated with higher incidence of myocardial infarction and death^[6,7]. Stent deployment in the main vessel (MV) "jails" this guidewire which then has to be pulled from underneath the stent struts. Polymer jacketed guidewires (PGW) have the advantage of maximum lubricity which allows them to be easily withdrawn from a jailed position. However there are concerns over wire damage and shearing of the polymer jacket^[8] and hence these are not universally recommended for

jailing^[9]. In addition, studies of pathological specimens have revealed evidence of embolized polymer in the myocardium^[10,11]. Guidewires with no or minimal polymer coatings are felt to be safer but run a risk of wire fracture during attempts at withdrawal^[12]. In a pilot study using scanning electron microscopy (SEM) at our institution, it was established that polymer shearing is a real phenomenon and that the amount of polymer sheared is weakly correlated with biomarker release post procedure^[13]. These studies have posed a question regarding an incremental risk of myonecrosis and possibly procedural myocardial infarction (PMI) with jailing of PGW and polymer shearing.

To try and answer this question, we performed a retrospective analysis of consecutive CBL interventions at our institution to determine if there is any association between type of guidewire jailed and PMI.

MATERIALS AND METHODS

All coronary interventions performed between January 2010 and October 2014 at our institution were reviewed to identify CBL interventions. Inclusion criteria were: CBL requiring percutaneous coronary intervention (PCI), MV diameter ≥ 2.5 mm and side branch diameter ≥ 2 mm. Criteria for exclusion were PCI for chronic total occlusions, cases where dual antiplatelet therapy was started after PCI and unavailability of biomarker levels at least 12 h after PCI. The Institutional Review Board of the University of Alabama at Birmingham approved the study. Chart review was performed to extract demographic and clinical parameters. Patients were divided into two groups based on occurrence of PMI as defined below.

Angiographic definitions

Angiograms were reviewed and quantitative measurements made using the CAAS system. A CBL was defined as a lesion located at a major coronary bifurcation point. Lesions were classified according to the Medina classification with a score of "1" or "0" being given to the proximal MV, distal MV and the SB components if they had $\geq 50\%$ diameter stenosis. Lesions were also classified as true bifurcation lesions (Medina type 1,1,1; 1,0,1 or 0,1,1) vs non-true bifurcation lesions (Medina type 1,0,0; 0,1,0 or 0,0,1).

Definition of procedural myocardial infarction

PMI was defined as creatine kinase (CK) MB $> 3 \times 99^{\text{th}}$ percentile of upper limit of normal post procedure if the pre-procedure levels were normal or a $> 20\%$ increase if pre-procedure levels were abnormal but stable or down-trending. If there were any unrelated cause for biomarker elevation, e.g., acute stent thrombosis, no reflow, SB occlusion, $< \text{TIMI } 3$ flow in MV or SB, shock or hypotension in the immediate 24 h post PCI, acute kidney injury, stroke, bleeding requiring transfusion, pulmonary embolism, access complication causing limb

Table 1 Demographic and clinical characteristics of the study population

	No PMI (n = 270)	PMI (n = 23)	P value
Age (yr)	63.6 ± 12.1	62.9 ± 14.4	0.80
Male sex	68.1%	60.9%	0.49
Smoking	55.6%	52.2%	0.86
Diabetes mellitus	33.0%	43.5%	0.36
Hypertension	78.1%	65.2%	0.33
Hyperlipidemia	73.7%	78.3%	0.87
Acute coronary syndrome	45.6%	52.2%	0.66

PMI: Procedural myocardial infarction.

ischemia or sustained arrhythmia these cases were classified as not having PMI. This was done to focus only on cases without a clear explanation for cause of PMI.

Statistical analysis

Continuous variables are represented as mean ± SD and compared using the Welch's *t* test as the sample sizes are unequal. Categorical variables were compared using the Fisher's exact test. Statistical analyses were carried out using SPSS v 22.0 (SPSS, Chicago, Illinois). Multivariate logistic regression was used to ascertain relationship of the following variables with PMI: Age, Diabetes Mellitus, severe lesion calcification, true bifurcation lesion, use of newer antiplatelet agent (Ticagrelor and Prasugrel), Bivalirudin use, upstream Glycoprotein IIb/IIIa use, use of preplanned two stent technique, SB protection with any guidewire and SB protection with PGW.

RESULTS

A total of 293 consecutive patients undergoing CBL interventions were included in the study. Seven point eight percent (*n* = 23) patients were classified as having had a PMI. Demographic and clinical characteristics of the patients broken down into two groups depending on whether or not PMI occurs are shown in Table 1. There were no statistically significant differences between the two groups. Table 2 shows the angiographic and procedural characteristics of patients with and without PMI. The most common bifurcation lesions included were left anterior descending/diagonal and left circumflex/marginal branch respectively. Proportion of true bifurcation lesions was higher and Bivalirudin use lower in the PMI group but these differences did not reach statistical significance. Seventy-four point four percent of total patients had a wire placed in the side branch and jailed with no difference amongst the two groups. However a jailed PGW was much more common in the PMI group (43.4% vs 15.9%, *P* = 0.003). There were no instances of wire entrapment or wire rupture in either group. The most common PGW jailed was a Hi Torque Whisper (Abbot Vascular, Abbott Park, IL, United States) while non PGW jailed were Runthrough NS

Table 2 Angiographic and procedural characteristics

	No PMI (n = 270)	PMI (n = 23)	P value
Vessels involved			0.68
LM bifurcation	15.9%	21.7%	
LAD/Diagonal	40.0%	47.8%	
LCX/OM	34.8%	21.7%	
RPDA/RPLA	8.8%	4.3%	
RCA/RV marginal	0.003%	0%	
Severe calcification	57.4%	65.2%	0.52
True bifurcation (Medina 1,1,1; 1,0,1; 0,1,1)	79.3%	91.3%	0.27
Main vessel diameter (mm)	3.3 ± 0.5	3.3 ± 0.4	0.4
Side branch diameter (mm)	2.6 ± 0.5	2.6 ± 0.4	0.94
Antiplatelet therapy			0.97
Plavix	73.7%	69.6%	
Prasugrel	7.0%	8.7%	
Ticagrelor	19.3%	21.7%	
Anticoagulant			0.08
Heparin	45.2%	65.2%	
Bivalirudin	54.8%	34.8%	
Upstream GpIIb/IIIa use	11.5%	13.0%	0.74
Planned 2 stent approach	28.1%	39.1%	0.34
Final kissing balloon angioplasty	45.9%	56.5%	0.39
SB protected	73.3%	87%	0.21
PGW jailed	15.9%	43.4%	0.003

PMI: Procedural myocardial infarction; PGW: Polymer jacketed guide wires.

(Terumo Interventional Systems, Somerset, NJ, United States), Cougar LS (Medtronic, Minneapolis, MN, United States) and HT Balance Middle Weight (BMW, Abbot Vascular, Abbott Park, IL, United States).

Univariate logistic regression analysis did not reveal any significant association of PMI with age, Diabetes, lesion calcification, use of newer antiplatelet agents, use of Bivalirudin, upstream use of Gp IIb/IIIa use, SB protection, pre-planned use of complex 2 stent strategy or Medina classification as true bifurcation lesion. The use of jailed PGW was strongly associated with PMI with an odds ratio of 4.1 (95%CI: 1.7-9.9; *P* = 0.002). Performing multivariate logistic regression to adjust for all the aforementioned factors still showed a strong association between jailing of PGW and PMI (Figure 1, Odds ratio 3.5; 95%CI: 1.2-9.9; *P* = 0.02).

DISCUSSION

SB protection is of considerable importance during CBL interventions. Occlusion of a SB > 1.0 mm has been associated with a 14% risk of MI^[6]. In a large series of 2227 CBL interventions, Hahn *et al*^[7] reported a SB occlusion rate of 8.4% and this increased the rate of major adverse cardiovascular events. The only protective factor found to prevent SB occlusion was the presence of a jailed guide-wire. Similar findings were reported in the Nordic study illustrating the importance of the jailed SB wire^[14]. The jailed guide wire provides a physical impediment to closure of the SB ostium and also facilitates re-wiring of the vessel by making the angle between the MV and the SB wider^[15]. Thus jailing

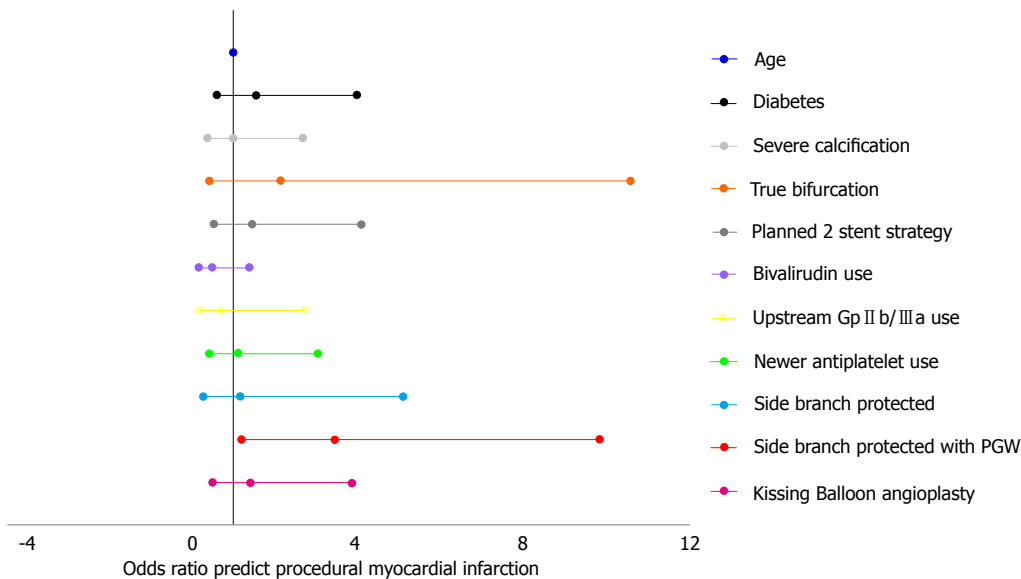


Figure 1 Multi-variate Odds ratios for various factors in predicting procedural myocardial infarction. PGW: Polymer jacketed guide wires.

a wire in the SB during MV stenting is a widely accepted practice for CBL interventions. However there is less consensus on the type of guide-wire to jail.

All coronary guide-wires have some degree of polymer coating on them with varying degrees of polymer cover or jacket. Based on the latter, guide-wires are broadly classified into three categories: (1) Wires with no polymer jacket - minimum lubricity, *e.g.*, HT BMW, Prowater and HT Floppy II; (2) Wires with intermediate polymer jacket - lack polymer jacket at the very distal end only; medium lubricity, *e.g.*, HT BMW Universal, Runthrough NS, Cougar LS; and (3) Wires with full polymer jacket - polymer jacket throughout the length of the wire; maximum lubricity; *e.g.*, HT Whisper, HT Pilot, HT Fielder XT.

PGW (3rd category) offer the attractive quality of lubricity and are easily withdrawn from underneath stent struts. However the interventional community has been wary of these as the initial reports of wire rupture were consistently with hydrophilic PGW^[8]. Since then multiple reports of non hydrophilic wires being entrapped have been published as well^[16-19]. With the lesser degree of lubricity of a non PGW, greater force may be required to extract the wire and hence risk deep intubation of the guide catheter and injury to the vessel as well.

Some reports have also raised the possibility of shearing of the polymer jacket during extraction of the jailed PGW^[20]. Grundeken *et al*^[11] examined the possibility of distal polymer embolization in two ways - they examined the aspirate from patients undergoing aspiration thrombectomy and reported that 45% samples had polymer material in them. Also, examination of autopsy specimens from patients who had undergone PCI showed intramyocardial polymer in 10% subjects. The amount of polymer detected increased as the polymer jacket increased with the maximum embolization noted in cases using HT Whisper

wires. This study is especially concerning because polymer embolization occurred even without jailing the guide-wire. It is notable that distal embolization of athero-emboli is considered an important contributor in the etiology of PMI^[21] - hence embolization of non-degradable polymer is a plausible hypothetical cause for PMI as well.

To try and quantify the extent of polymer shearing and embolization, we have previously performed a small study examining jailed HT Whisper and Runthrough NS wires with SEM^[13]. This revealed polymer shearing in both types of wires but up to 5 fold higher in the HT Whisper, a PGW. Amount of polymer shearing was also weakly correlated with the level of CK MB post procedure. Pan *et al*^[22] randomized 235 patients who underwent CBL interventions with the jailed wire technique to use of PGW or non PGW and examined the jailed wires using an optical microscope. They reported more structural damage to non PGW although no wire fracture was noted. It should be noted though that the study used magnification up to 6.3X only, which is insufficient to detect shearing of polymer and also used wires with no polymer cover as the comparison group, the use of which has gone down in comparison to wires with intermediate polymer cover. Also, the rate of PMI was not different in the two groups.

In this respect, our study is the second study to investigate the relationship of type of wire jailed to PMI. Our results show a strong association of jailed PGW to PMI which are contrary to the results of Pan *et al*^[22]. One reason may be that there are varied reasons why patient have elevated cardiac biomarkers post PCI. Some of these may be no reflow phenomenon, distal athero-embolization, occlusion of SB, coronary perforation, development of cardiogenic (or other types of) shock, access complications causing limb ischemia, arrhythmias, bleeding causing hemodynamic instability,

etc. These, at least by our current knowledge of PMI are more likely to be contributors than polymer embolization from jailed PGW. Hence we meticulously excluded all cases which may have had any confounding factor causing a biomarker elevation and categorized these cases as having no PMI. This further strengthens our belief in the credibility of our results.

Limitations

Our study has all the limitations of a retrospective analysis and the inherent biases. However we have attempted to correct these biases by careful data acquisition, exclusion of cases with potential confounding factors and a multivariate logistic regression analysis. We also note that the definition of PMI used is inconsistent with the 3rd universal definition of MI consensus document^[23] which defines PMI as $> 5 \times \text{ULN}$ of cardiac Troponin (cTn) along with symptoms, electrocardiographic, imaging or angiographic evidence of ischemia. Multiple studies have been done that question the relevance of the $5 \times \text{ULN}$ of cTn criterion as a $> 3 \times \text{ULN}$ of CK-MB cut-off is better correlated with mortality^[24] and evidence of new myocardial injury as detected by cardiac MRI^[25]. In fact, a cut off of $3 \times \text{ULN}$ of CK-MB is equivalent to a cut-offs of $20 \times \text{cTn}$ for mortality and $40 \times \text{cTn}$ for MRI proven new myocardial injury. Hence while the updated definition is valid in conjunction with clinical evidence of ischemia, CK MB may be a better choice for isolated biomarker analyses.

In conclusion, our study shows that jailed PGW may be associated with a threefold higher risk of PMI. Given the retrospective design, this finding should be treated as hypothesis generating and hopefully will trigger prospective analysis to confirm or refute this association. The etiology for this risk is believed to be polymer shearing and micro-embolization which has been proven by multiple small but rigorously conducted studies^[11,13]. We believe that much has to be learned about the potential role of polymer shearing and embolization in myonecrosis post CBL intervention. There is also a need to determine if the wires with intermediate polymer cover may be the best middle path compromise in the argument of lubricity vs fracture and polymer shearing.

COMMENTS

Background

Polymer jacketed guide wires (PGW) are frequently used for side branch protection during bifurcation coronary interventions. Their lubricity is an attractive property for this use as it makes them easy to retract from underneath stent struts. However, microscopic shearing of polymer from jailed guide wires has been reported and may be a potential cause of procedural myocardial infarction (PMI) as this may cause distal micro-embolization. Hence, the authors performed a retrospective analysis of bifurcation interventions at this institution to ascertain relationship of PGW use with PMI.

Research frontiers

PMI has important prognostic implications in patients undergoing percutaneous coronary intervention. Thus it is important to understand if any procedural factors such as use of PGW have any effect on PMI.

Innovations and breakthroughs

This is only the second study to ascertain if there is a relationship between use of jailed PGW and PMI. In their data there is a strong association of these which translates to a three fold higher risk of PMI if a PGW is jailed.

Applications

These results should caution interventional cardiologists from adopting PGW as their go to wire for jailing until prospective data comparing different types of wires are available. Randomized studies are needed to compare newer generation non polymer jacketed, intermediate polymer jacketed and full polymer jacketed coronary guide wires.

Terminology

PGW: Polymer jacketed guide wires; PMI: Procedural myocardial infarction.

Peer-review

This is an interesting manuscript about the relation of jailing PGW to PMI. The authors demonstrated that jailed PGW might be associated with PMI. This manuscript is nicely structured and well written.

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Observational Study

Markers of inflammation and cardiovascular disease in recently diagnosed celiac disease patients

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Abstract

AIM

To evaluate novel risk factors and biomarkers of cardiovascular disease in celiac disease (CD) patients compared with healthy controls.

METHODS

Twenty adult patients with recent diagnosis of CD and 20 sex, age and body mass index-matched healthy controls were recruited during a period of 12 mo. Indicators of carbohydrate metabolism, hematological parameters and high sensitive C reactive protein were determined. Moreover, lipoprotein metabolism was also explored through evaluation of the lipid profile and

the activity of cholesteryl ester transfer protein and lipoprotein associated phospholipase A2, which is also considered a specific marker of vascular inflammation. The protocol was approved by the Ethic Committee from School of Pharmacy and Biochemistry, University of Buenos Aires and from Buenos Aires Italian Hospital, Buenos Aires, Argentina.

RESULTS

Regarding the indicators of insulin resistance, CD patients showed higher plasma insulin levels [7.2 (5.0-11.3) mU/L *vs* 4.6 (2.6-6.7) mU/L, $P < 0.05$], increased Homeostasis Model Assessment-Insulin Resistance [1.45 (1.04-2.24) *vs* 1.00 (0.51-1.45), $P < 0.05$] and lower Quantitative Sensitive Check index [0.33 (0.28-0.40) *vs* 0.42 (0.34-0.65), $P < 0.05$] indexes. Folic acid concentration [5.4 (4.4-7.9) ng/mL *vs* 12.2 (8.0-14.2) ng/mL, $P < 0.01$] resulted to be lower and High-sensitivity C reactive protein levels higher (4.21 ± 6.47 mg/L *vs* 0.98 ± 1.13 mg/L, $P < 0.01$) in the patient group. With respect to the lipoprotein profile, CD patients showed lower high density lipoprotein-cholesterol (HDL-C) (45 ± 15 mg/dL *vs* 57 ± 17 mg/dL, $P < 0.05$) and apo A-I (130 ± 31 mg/dL *vs* 155 ± 29 mg/dL, $P < 0.05$) levels, as well as higher total cholesterol/HDL-C [4.19 (3.11-5.00) *vs* 3.52 (2.84-4.08), $P < 0.05$] and apo B/apo A-I (0.75 ± 0.25 *vs* 0.55 ± 0.16 , $P < 0.05$) ratios in comparison with control subjects. No statistically significant differences were detected in lipoprotein-associated lipid transfer protein and enzymes.

CONCLUSION

The presence and interaction of the detected alterations in patients with CD, would constitute a risk factor for the development of atherosclerotic cardiovascular disease.

Key words: Inflammation; Cardiovascular disease; High density lipoprotein-cholesterol; Lipoproteins; Celiac disease

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Core tip: Given that data about the presence of metabolic alterations and atherogenic risk factors in celiac disease are scarce and contradictory, we aimed to investigate carbohydrate metabolism, lipoprotein profile and inflammatory status in patients with celiac disease (CD). Patients presented higher insulin levels, Homeostasis Model Assessment-Insulin Resistance index, apo B/apo A-I ratio and High-sensitivity C reactive protein concentration, as well as lower Quantitative Sensitive Check index index, high density lipoprotein-cholesterol and apo A-I levels in comparison with sex and aged-matched healthy controls. Persistence of these alterations through long periods of time in a chronic pathologic condition, as it is the case with CD, would constitute a high risk of developing atherosclerotic cardiovascular disease.

Tetzlaff WF, Meroño T, Menafrá M, Martín M, Botta E, Matoso MD, Sorroche P, De Paula JA, Boero LE, Brites F. Markers of inflammation and cardiovascular disease in recently diagnosed celiac disease patients. *World J Cardiol* 2017; 9(5): 448-456 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i5/448.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i5.448>

INTRODUCTION

Celiac disease (CD) is a multisystemic disease which mainly affects the digestive system, though not exclusively. Its main trait is chronic and diffuse inflammation of the mucosa of the small intestine and it can present a wide variety of clinical symptoms^[1]. Thus far, the only available therapy for CD consists of the implementation of a gluten free diet (GFD), whose efficacy depends on strict adherence.

It is remarkable that most cases of CD lack typical gastrointestinal symptoms and are, instead, very frequently associated with presentations known as atypical or extra-intestinal. Thus, its diagnosis represents one of the main challenges for health professionals^[2].

Commonly, CD has been associated with certain physiopathological conditions (type 1 diabetes, Hashimoto thyroiditis, *etc.*) which are not directly related to gluten ingestion^[3]. Among these conditions, it is worth noting that the evidence linking CD and atherosclerotic cardiovascular disease (CVD) is scarce. It is well known that CD patients do not show classical CVD risk factors. In fact, hypertension and hypercholesterolemia are less frequent in CD patients than in the general population^[4]. However, previous studies have failed to show lower CVD risk in CD patients than in healthy subjects^[4,5]. Furthermore, an important study carried out in Sweden in approximately 14000 hospitalized CD patients showed higher risk of acute myocardial infarction, chest angina, cardiac insufficiency, brain hemorrhage and ischemic stroke when compared to sex and age-paired healthy controls^[6].

These facts suggest that CD would be associated with novel atherogenic risk factors or even with other non-identified risk factors. In fact, inflammation and anemia, among other signs that characterize CD, could represent a link between this pathology and CVD^[7,8].

Atherosclerosis is presently understood as a chronic inflammatory disease in which endothelial dysfunction and biomarkers of inflammation are present since the early stages of the pathology^[9]. So far, the inflammatory process typical of CD has not been described in relation to increased risk of CVD.

The aim of the present study was to evaluate novel risk factors and biomarkers of CVD in CD patients in comparison to sex, age and body mass index (BMI)-matched healthy controls. In addition, the metabolic differences between patients with typical and atypical presentations of the disease were also analyzed.

MATERIALS AND METHODS

Subjects

Twenty patients with CD were consecutively recruited from the service of gastroenterology, Buenos Aires Italian Hospital, during a period of 12 mo. The inclusion criteria were adult age and recent diagnosis of CD (< 3 mo) based on histopathological findings and serological markers (anti-gliadin IgG and IgA and anti-transglutaminase IgA). Patients were not treated and they had not still started a GFD. All individuals presenting any other intestinal inflammatory disease, IgA deficiency, malignant diseases, chronic infections, pregnancy, thyroid, renal or hepatic alterations, history of CVD, smoking, alcohol consumption > 40 g/d, and treatment with drugs known to affect lipid and/or carbohydrate metabolism were excluded. Patients were classified according to the presence of gastrointestinal (typical presentation) or extra-digestive symptoms (atypical presentation)^[2]. Gastrointestinal manifestations analyzed were: Diarrhea, abdominal distention, weight loss, and malabsorption syndrome. Extra-digestive alterations considered were: Anemia, mouth ulcers, osteoporosis, and modifications of liver function tests. Employing these criteria, 11 out of the 20 CD patients showed gastrointestinal symptomatology and 9 showed only extradiigestive symptoms. The group of CD patients was compared with a sex, age and BMI-matched group of healthy volunteers ($n = 20$). Weight, height and waist circumference were registered in all subjects and an exhaustive anamnesis was performed. All participants in the study signed an informed consent. The protocol was approved by the Ethical Committees from School of Pharmacy and Biochemistry, University of Buenos Aires and from Buenos Aires Italian Hospital. Buenos Aires, Argentina.

Study protocol and samples

Blood samples were obtained from the antecubital vein after 12 h of fasting. Serum and EDTA plasma (final EDTA concentration 1 mg/mL) were prepared from venous blood collected into sterile, evacuated tubes. The former was centrifuged at 1500 g for 15 min at 4 °C. Serum was isolated and stored at 4 °C and -70 °C.

Determination of general biochemical parameters

Plasma concentrations of glucose, urea, uric acid, total bilirubin, folic acid and vitamin B12, as well as aspartate aminotransferase (ASAT), alanin aminotransferase and alkaline phosphatase activities, and hemogram were determined by standardized methods. Insulin levels were measured by radioimmunoassay (Diagnostics Products Corp., Los Angeles CA, United States). Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) was calculated using the formula $[\text{glucose (mmol/L)} \times \text{insulin (uU/mL)}] / 22.5$ and Quantitative Sensitive Check index (QUICKI) using the formula $1 / [\ln \text{Glucose (mmol/L)} + \ln \text{Insulin (mU/L)}]$ ^[10,11]. High-sensitivity

C reactive protein (hsCRP) levels were determined by immunoturbidimetry (Roche, Mannheim, Germany) in a Hitachi 917 autoanalyzer (Tokyo, Japan).

Determination of the lipid, lipoprotein and apolipoprotein profile

Plasma levels of total cholesterol (TC) and triglycerides were quantified by standardized methods (Roche, Mannheim, Germany) in a Hitachi 917 autoanalyzer (Tokyo, Japan). High density lipoproteins (HDL) were isolated from the supernatant obtained after selective precipitation of apolipoprotein (apo) B-containing lipoproteins using 0.44 mmol/L phosphotungstic acid in presence of magnesium ions^[12]. Cholesterol (C) of low density lipoprotein (LDL) was estimated as the difference between TC and the cholesterol contained in the supernatant obtained after selective precipitation of LDL with 10 g/L polyvinil sulfate in polyethilenglicol (600 Da; 2.5 w/v; pH = 6.7)^[13]. Non HDL-C was calculated as the difference between TC and HDL-C. Very low density lipoprotein cholesterol (VLDL-C) was calculated as the difference between the supernatants of the LDL-C and HDL-C precipitations. Apo B and apo A-I levels were quantified by immunoturbidimetry (Roche, Mannheim, Germany) in a Hitachi 917 autoanalyzer (Tokyo, Japan). Results were expressed as mg/dL. The following ratios were calculated: TG/HDL-C, TC/HDL-C and apo B/apo A-I.

Determination of cholesteryl ester transfer protein activity

Cholesteryl ester transfer protein (CETP) activity was evaluated in serum samples following the radiometric method previously described with minor modifications^[14]. Briefly, the capacity of the serum to promote the transfer of tritiated esterified cholesterol (EC) from the biosynthetically marked HDL3 subfraction (³H-EC-HDL3) (NEN Life science products, Boston, United States) to apo B containing lipoproteins present in the serum. Serum samples were incubated with ³H-CE-HDL3 (50 μmol/L cholesterol) with iodoacetate (1.5 mmol/L) in TBS buffer (pH = 7.4) during 3 h at 37 °C. After incubation, apo B-containing lipoproteins were separated from HDL by selective precipitation with phosphotungstic acid (0.44 mmol/L) in the presence of magnesium ions. Radioactivity was measured in the reaction cocktail and in the supernatant containing the HDL subfraction in a liquid scintillation counter (Packard 210 TR, Packard Instruments, Meridians, CT, United States). Results were expressed as the percentage of tritiated EC transferred from HDL3 to apo B-containing lipoproteins, per ml, per hour. All samples were processed in the same assay.

Determination of lipoprotein associated phospholipase A2 activity

Lipoprotein associated phospholipase A2 activity (Lp-PLA2) was evaluated employing the radiometric assay described by Blank *et al.*^[15] with minor modifications.

Table 1 Clinical and biochemical characteristics from patients with celiac disease and control subjects

	Patients with celiac disease (<i>n</i> = 20)	Control subjects (<i>n</i> = 20)	<i>P</i>
Age (yr)	50 (25-58)	47 (28-60)	ns
Men/woman	5/15	5/15	ns
BMI (kg/m ²)	22.8 (20.4-26.2)	23.0 (21.0-24.7)	ns
Glucose (mg/dL)	87 ± 11	86 ± 12	ns
Insulin (mU/L)	7.2 (5.0-11.3)	4.6 (2.6-6.7)	< 0.05
HOMA-IR	1.45 (1.04-2.24)	1.00 (0.51-1.45)	< 0.05
QUICKI	0.33 (0.28-0.40)	0.42 (0.34-0.65)	< 0.05
Urea (mg/dL)	27 (21-34)	35 (34-39)	< 0.01
Creatinine (mg/dL)	0.74 (0.63-0.88)	0.80 (0.75-1.10)	< 0.05
Uric acid (mg/dL)	5.0 ± 1.2	4.3 ± 1.6	ns
Bilirubin (mg/dL)	0.7 (0.5-0.8)	0.6 (0.6-0.8)	ns
ASAT (U/L)	26 (20-35)	14 (12-20)	< 0.01
ALAT (U/L)	22 (17-39)	18 (16-22)	ns
ALP (U/L)	80 (59-102)	124 (67-219)	ns

BMI: Body mass index; HOMA-IR: Homeostasis Model Assessment insulin resistance; QUICKI: Quantitative insulin sensitivity check index; ASAT: Aspartate-amine transferase; ALAT: Alanine-amine transferase; ALP: Alkaline phosphatase; ns: Non significant. Data are shown as mean ± SD or median (interquartile range) according to data distribution.

The extraction of the marked acetate was performed using chloroform and the radioactivity of the aqueous phase was measured in a liquid scintillation counter (Packard 210 TR, Packard Instruments, Meridians, CT, United States). The radioactivity of the reaction buffer was also measured. Results were expressed as μmol of acetate liberated, per millilitre, per hour. All samples were processed in the same assay.

Statistical analysis

The sample size was calculated based on previous studies carried out in our laboratory. The outcome variables chosen to perform the sample size calculation for this study were HDL-C, CETP and Lp-PLA2. Having defined a 0.8 power, an effect size of 1.0 and a significance level of 0.05, the number of patients to be included in the present study was at least 17. Data distribution was analyzed with the Shapiro-Wilks test and data was expressed as mean ± SD, if distribution was found to be parametric, or as median (interquartile range) if distribution was non-parametric. To assess differences between groups, both parametric and non-parametric methods were employed. Correlation analyses were performed using Spearman or Pearson tests depending on variable distribution. When partial correlations, linear regressions or adjusted group differences were performed, all non-parametric variables were normalized prior to be included in the analysis. Statistical significance was defined as *P* < 0.05. A statistical review of the study was performed by a biomedical statistician. For the statistical analysis, the programs Infostat (Universidad Nacional de Cordoba, Argentina) and SPSS 19.0 (IBM, Chicago, United States) were used.

Table 2 Hematological parameters from patients with celiac disease and control subjects

	Patients with celiac disease (<i>n</i> = 20)	Control subjects (<i>n</i> = 20)	<i>P</i>
Erythrocytes (10 ⁶ /mL)	4.40 ± 0.48	4.58 ± 0.27	ns
Hematocrite (%)	38.5 ± 4.0	40.1 ± 2.6	ns
Hemoglobin (g/dL)	13.0 ± 1.4	13.3 ± 0.9	ns
Serum iron (μg/dL)	73 ± 35	105 ± 61	ns
Ferritin (ng/mL)	33 (13-110)	92 (43-117)	ns
Transferrin (mg/dL)	261 ± 62	293 ± 59	ns
Transferrin Sat. (%)	25 ± 14	29 ± 14	ns
Vitamin B12 (pg/mL)	337 (251-482)	315 (265-393)	ns
Folic acid (ng/mL)	5.4 (4.4-7.9)	12.2 (8.0-14.2)	< 0.01

ns: Non significant; Sat.: Saturation. Data are shown as mean ± SD or median (interquartile range) according to data distribution.

RESULTS

As expected, CD patients and control subjects did not show any difference in age, sex distribution and BMI (Table 1). Nevertheless, CD patients had significantly higher insulin levels and HOMA-IR, as well as lower QUICKI (Table 1). Both urea and creatinine concentrations were lower in the patient group, though individual results were comprised within the reference values. Additionally, ASAT activity was significantly increased in patients compared to controls.

The evaluation of hematological parameters showed no significant decrease in hemoglobin concentration in patients. Furthermore, only one woman met the criteria for anemia diagnosis (hemoglobin < 12 g/dL for women and < 13 g/dL for men). Similarly, there were no differences in total iron content, transferrin saturation or concentrations of ferritin, transferrin and vitamin B12. Only folic acid concentration was found to be significantly lower in patients (Table 2). Employing the reference values established by the World Health Organization^[16,17], the prevalence of folic acid deficiency resulted to be 10% (< 4 ng/dL), of iron deficiency 15% (ferritin < 15 ng/dL) and of low vitamin B12 7.5% (< 203 pg/mL).

Regarding the lipid and lipoprotein profile, no differences were detected in TG, TC, LDL-C and apo B levels. However, statistically significant decreases in HDL-C and apo A-I concentrations were observed (Table 3). Furthermore, both parameters showed a strong positive correlation between them (*r* = 0.78; *P* < 0.0001). TC/HDL-C and apo B/apo A-I ratios, both of which possess high predictive value for CVD, were significantly higher in patients, whilst TG/HDL-C showed no difference between groups. On the other hand, CETP activity was similar in patients and controls (145% ± 32%/mL.h vs 132% ± 33%/mL.h, *P* > 0.05) and exhibited direct correlations with TG levels (*r* = 0.52; *P* < 0.005) and apo B/apo A-I ratio (*r* = 0.48; *P* < 0.005), and negative ones with HDL-C (*r* = -0.58; *P* < 0.0001) and apo A-I (*r* = -0.40; *P* < 0.005).

Table 3 Lipid, lipoprotein and apolipoprotein profile from patients with celiac disease and control subjects

	Patients with celiac disease (n = 20)	Control subjects (n = 20)	P
TG (mg/dL)	81 (65-119)	78 (60-114)	ns
TC (mg/dL)	185 ± 37	194 ± 39	ns
VLDL-C (mg/dL)	18 ± 8	17 ± 7	ns
LDL-C (mg/dL)	139 (89-149)	107 (95-147)	ns
HDL-C (mg/dL)	45 ± 15	57 ± 17	< 0.05
Non-HDL-C (mg/dL)	153 (105-167)	137 (112-167)	ns
Apo A-I (mg/dL)	130 ± 31	155 ± 29	< 0.05
Apo B (mg/dL)	93.6 ± 23.8	83.5 ± 20.7	ns
TG/HDL-C	2.09 (1.13-2.98)	1.29 (1.06-1.93)	ns
TC/HDL-C	4.19 (3.11-5.00)	3.52 (2.84-4.08)	< 0.05
ApoB/apo A-I	0.75 ± 0.25	0.55 ± 0.16	< 0.01

TG: Triglycerides; TC: Total cholesterol; VLDL: Very low density lipoprotein; LDL: Low density lipoprotein; HDL: High density lipoprotein; apo: Apolipoprotein; ns: Non significant. Data are shown as mean ± SD or median (interquartile range) according to data distribution.

Evaluation of inflammation markers showed an increase in hsCRP levels in CD patients (Figure 1), which also correlated with apo B/apo A-I ratio ($r = 0.42$; $P < 0.01$). Even though white blood cell count (WBC) showed no differences between the two groups ($6.11 \pm 1.31 \times 10^3/\text{mL}$ vs $6.17 \pm 1.15 \times 10^3/\text{mL}$), it was directly associated with several parameters of the lipid profile (r/p ; TG, $0.33/< 0.05$; HDL-C, $-0.34/< 0.05$; apo B, $0.42/< 0.05$; TG/HDL-C, $0.37/< 0.05$; TC/HDL-C, $0.44/< 0.01$; and apo B/apo A-I, 0.51 ; < 0.005). Lastly, Lp-PLA2 activity was similar between patients and controls ($7.20 \pm 1.28 \mu\text{mol/mL.h}$ vs $7.91 \pm 2.02 \mu\text{mol/mL.h}$) and was positively associated with LDL-C, main carrier of the enzyme in circulation ($r = 0.50$; $P < 0.005$).

Moreover, folic acid level was significantly associated with several parameters of the lipid profile (r/p ; HDL-C, $0.52/< 0.05$; apo A-I, $0.45/< 0.01$; TG/HDL-C, $-0.36/< 0.05$; and apo B/apo A-I, $-0.34/< 0.05$) and with hsCRP concentration ($r = -0.42$; $P < 0.05$).

When comparing patients according to the clinical features, no differences were detected between patients with typical and atypical presentation of the disease in any of the parameters analyzed (data not shown).

DISCUSSION

Patients with CD showed a slight alteration in carbohydrate metabolism, decreased folic acid levels, a more atherogenic lipoprotein profile and an increase in the inflammatory marker hsCRP, with no difference evidenced between typical and atypical presentation of the disease. Likely, in both groups, the severity of duodenal lesion would not be a determining factor in the metabolic alterations nor in the increase of hsCRP observed in this study.

Unlike other pathologies characterized by the presence of systemic inflammation, such as lupus erythematosus and rheumatoid arthritis, in which patients

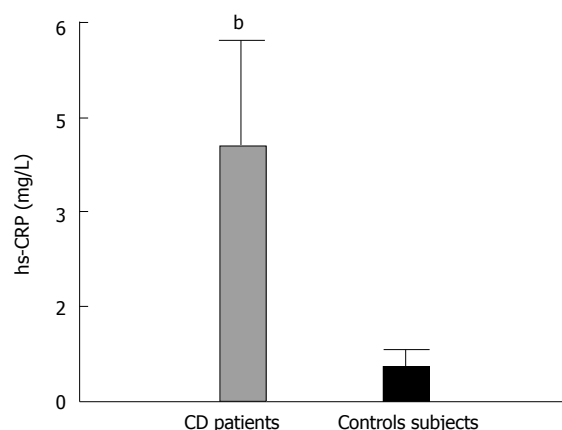


Figure 1 Levels of high sensitive C-reactive protein in patients with celiac disease (n = 20) and control subjects (n = 20). ^b $P < 0.01$. hsCRP: High sensitive C reactive protein; CD: Celiac disease.

show higher CVD morbidity and mortality^[18,19], available evidence for CD appears less solid and more controversial. Even though some studies have described an increase in CVD risk compared with the general population^[20-22], this has not been the case in other reports^[4,23]. A group of CD patients, retrospectively studied in comparison with data from general population^[24], showed less CVD risk employing the Framingham score. Nevertheless, assessment of cardiac functionality, specifically of the left ventricle^[25], and the study of the presence of subclinical atherosclerosis, analyzed through aortic stiffness, aortic strain, and aortic distensibility^[26,27], evidenced a clear association between CD and CVD. Moreover, a previous study showed higher carotid intima media thickness (an established marker of generalized atherosclerosis that correlates with the extent of coronary artery disease and predicts future cardiovascular events) in CD patients compared to healthy controls and similar to that of patients with type 1 diabetes^[28]. Lastly, it is worth noting that a recent meta-analysis^[29], based on ten studies performed in CD patients, showed a slight increase in the risk of stroke, acute myocardial infarction, and cardiovascular death, though only in the first case this increase reached statistical significance. As evidenced by the bibliography, the subject remains highly controversial.

In CD patients, a systemic pro-inflammatory status was evidenced through an increase in plasma hsCRP levels. According to the guides of the American Heart Association^[30], values above 3 mg/dL, such as those observed in the group of the CD patients studied, would be indicative of high CVD risk. Even though Lp-PLA2 activity, considered a specific marker of vascular inflammation^[31], showed no differences between patients and controls, there is solid evidence about the increase of other inflammation markers in CD. In this regard, a previous study reported an increase in tumor necrosis factor (TNF)- α -producing innate lymphoid cells in the intestinal mucosa of untreated CD patients in comparison with treated patients and healthy controls^[32].

Moreover, an increase in TNF- α and interleukin (IL)-6 levels has been reported in the epithelium and the lamina propria of the intestinal mucosa of untreated CD patients^[33,34]. Additionally, higher levels of IL-6 have been observed in the plasma of untreated CD patients compared to treated ones and healthy controls^[35,36].

Regarding markers of carbohydrate metabolism, even though insulin levels and HOMA-IR were increased and QUICKI diminished, the analysis of the individual values did not allow the diagnosis of insulin resistance in any of the patients included in the present study. In fact, the results obtained were below the values reported for patients with metabolic syndrome or type 2 diabetes, though above those reported for the general population^[37-40]. Nevertheless, even the presence of a subtle alteration in carbohydrate metabolism in untreated CD patients would possess great clinical impact. Actually, GFD, the only available treatment for CD, contains higher caloric density than similar diets based on gluten containing foods, and its implementation could, as a result, increase the risk of developing obesity, and, consequently, metabolic syndrome and diabetes^[41-43]. Therefore, assessment of fasting glucose and insulin in patients diagnosed with CD before and during the introduction of GFD should be performed. However, the subject is still controversial. Kabbani *et al.*^[44] reported lower prevalence of metabolic syndrome and type 2 diabetes in patients under GFD treatment, regardless of treatment duration. Moreover, experiments carried out in C57BL/6 mice fed on a hyper fat diet with and without gluten showed that GFD reduced insulin resistance, adiposity and inflammation^[45], although it is necessary to consider that these mice did not present CD. In the present study, the finding of significantly higher insulin levels and HOMA-IR and lower QUICKI than in controls suggests the presence of a slightly altered carbohydrate metabolism, which could be related to the pro-inflammatory status described in CD patients and evidenced in our study by higher hsCRP levels. It has been previously proposed that inflammation could be a causative agent for alterations in carbohydrate metabolism through the action of cytokines such as TNF- α , IL-6 and IL-1 β , among others^[46,47].

Studying lipoprotein profile in CD patients appears interesting, since there is evidence for both a decrease in cholesterol absorption and an increase in its synthesis^[48-50]. In the current study, patients showed TC and LDL-C levels similar to controls. These findings are in disagreement with the decrease in both parameters previously reported for CD patients^[5,51,52]. Patients evaluated in this study also presented lower HDL-C levels. There is prior evidence showing a 12% prevalence of CD in patients with low HDL-C concentration^[53], much higher than that reported for the general population, which implies a causal relationship between the presence of CD and the decrease in HDL-C. Unlike in the case of patients with insulin resistance^[54,55], this decrease was not found to be associated with higher CETP activity. Therefore,

this alteration could result from a lower synthesis and secretion of apo A-I^[56]. Furthermore, longitudinal studies described an increase in HDL-C and apo A-I values after initiation of treatment with GFD^[51]. In addition, CD patients presented an increase in TC/HDL-C and apo B/apo A-I ratios^[57], which reflect an imbalance between proatherogenic and antiatherogenic lipid factors. Another possibility that could explain HDL-C decrease is that HDL particles from CD patients would possess less capability to promote cholesterol efflux from cells. In fact, apo A-I has not only got a structural role in HDL particles, but it is also involved in multiple antiatherogenic functions including cholesterol efflux promotion^[58]. Due to the decrease in intestinal apo A-I synthesis, the number of circulating HDL particles would be diminished and, in turn, each particle would be depleted in this apolipoprotein. As a matter of fact, in other inflammatory pathologies such as rheumatoid arthritis, alterations in HDL functionality have been associated with higher risk of CVD^[59]. Study of HDL functions in affected patients could provide important evidence linking CD and CVD risk.

Regarding hematological parameters, only folic acid was decreased in CD patients. This finding is consistent with previous reports that show a decrease in folic acid levels as a consequence of impaired intestinal absorption, resulting from the damage to the intestinal epithelium caused by the inflammatory process^[60]. This folic acid deficiency persists, in many cases, even after the initiation of treatment with GFD^[61]. It is worth noting that a decrease in folic acid levels may lead to an increase in homocysteine concentration. One of the main homocysteine clearance pathways consists of its re-methylation and recycling to methionine, a process catalyzed by the methionine synthase (MTR) enzyme, which links the folate cycle with homocysteine metabolism^[62]. In fact, different studies showed higher homocysteine levels in CD patients^[26,63,64]. Importantly, this increment was independently associated with increased risk and severity of coronary artery disease^[65]. Moreover, high homocysteine levels were also identified as independent predictors of a suboptimal response to antiplatelet therapy with acetyl salicylic acid, thus favouring thrombotic complications in patients with coronary artery disease^[66]. In addition, in a meta-analysis of randomized controlled trials, Liu *et al.*^[67] demonstrated that folic acid supplementation could improve the endothelial dysfunction observed in patients with coronary artery disease. Nevertheless, studies on homocysteine-lowering interventions with vitamin B6, folic acid (vitamin B9) or vitamin B12, administered alone or in combination with the purpose of preventing cardiovascular events, failed to consistently demonstrate their efficacy^[68]. Therefore, consideration of increased homocysteine levels as a risk factor for CVD is still a controversial topic^[69].

In the present study, newly diagnosed CD patients, who were not following a GFD, presented higher insulin

levels, HOMA-IR index, apo B/apo A-I ratio and hsCRP concentration, as well as lower QUICKI index, HDL-C and apo A-I levels in comparison with sex and age-matched healthy controls.

Limitations

The main limitation of the present study is that, due to its cross-sectional design, it only provides a “snapshot” of the outcome and the characteristics associated with it, at a specific point in time. Then, only associations that may exist and are therefore useful in generating hypotheses for future research may be established. Another limitation is the sample size, which may be attributed to the fact that this study only included newly diagnosed CD patients, but that hampered the search for a possible correlation between intestinal inflammation factors and the risk of atherosclerosis.

Conclusions

According to the results reported in the current study, untreated CD patients would present modifications in carbohydrate and lipoprotein metabolism and a pro-inflammatory status. Even though the magnitude of the alterations here described is not major, their presence and interaction through long periods of time in a chronic pathologic condition, as it is the case with CD, would constitute a high risk of developing atherosclerotic CVD.

COMMENTS

Background

Celiac disease (CD) is a multisystemic disease which main trait is chronic and diffuse inflammation of the mucosa of the small intestine. The only available therapy for CD consists of the implementation of a gluten free diet (GFD). It is well known that CD patients do not show classical cardiovascular disease (CVD) risk factors suggesting that CD would be associated with novel atherogenic risk factors or even with other non-identified risk factors such as inflammatory markers.

Research frontiers

The role of novel atherogenic risk factors or inflammatory markers for CVD in CD patients has been poorly studied. The research hotspot is to assess which factors or markers for cardiovascular disease are found in CD patients in order to be able to prevent or treat them.

Innovations and breakthroughs

It is well known that CD patients do not show classical CVD risk factors. Therefore in these patients, detection of novel atherogenic risk factors would be crucial to reduce the risk of CVD.

Applications

The detection of CVD risk factors in CD patients is an important tool for the implementation of an adequate treatment.

Terminology

CD is a disease which mainly affects the digestive system. Its main trait is chronic and diffuse inflammation of the mucosa of the small intestine and it can present a wide variety of clinical symptoms. It is remarkable that most cases of CD lack typical gastrointestinal symptoms and are, instead, very frequently associated with presentations known as atypical or extra-intestinal. Thus, its diagnosis represents one of the main challenges for health professionals

Peer-review

This is an interesting study showing that patients with CD do have an atherogenic lipoprotein profile that may dispose them to develop CVD.

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Prospective Study

Combined assessment of myocardial damage and electrical disturbance in chronic heart failure

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Abstract

AIM

To investigate feasibility of combined assessment of biochemical and electrophysiological myocardial impairment markers risk-stratifying patients with chronic heart failure (CHF).

METHODS

Serum levels of heart-type fatty acid binding protein (H-FABP) as a marker of ongoing myocardial damage and QRS duration on electrocardiogram were measured at admission in 322 consecutive patients with CHF. A prolonged QRS duration was defined as 120 ms or longer. The cut-off value for H-FABP level (4.5 ng/mL) was determined from a previous study. Patients were prospectively followed during a median follow up period of 534 d. The primary endpoint was cardiac deaths and rehospitalization for worsening CHF.

RESULTS

There were 117 primary events, including 27 cardiac deaths and 90 rehospitalizations. Patients were stratified into four groups according to H-FABP level and QRS duration (≥ 120 ms). Multivariate analysis demonstrated that high H-FABP levels [hazard ratio (HR) = 1.745, $P = 0.021$] and QRS prolongation (HR

1.612, $P = 0.0258$) were independent predictors of cardiac events. Kaplan-Meier analysis demonstrated that the combination of high H-FABP levels and QRS prolongation could be used to reliably stratify patients at high risk for cardiac events (log rank test $P < 0.0001$).

CONCLUSION

Combined assessment of myocardial damage and electrical disturbance can be used to risk-stratify patients with CHF.

Key words: QRS prolongation; Heart-type fatty acid binding protein; Heart failure; Prognosis

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Core tip: This was a prospective single center study with 322 consecutive patients with chronic heart failure (CHF) seeking to evaluate the feasibility of combined assessment of biochemical and electrophysiological markers of myocardial impairment for risk-stratifying patients with CHF. QRS prolongation and high heart-type fatty acid binding protein levels are independently associated with cardiac events in patients with CHF.

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INTRODUCTION

Chronic heart failure (CHF) is a major health problem with high mortality despite advance in medical therapy^[1-3]. Various pathophysiological changes are reportedly associated with initiation and progression in CHF^[4]. The role of biomarkers continues to increase in importance to evaluate and risk-stratify CHF patients^[5].

Heart-type fatty acid binding protein (H-FABP) is a small molecule protein (14-15 kDa), abundant in cytoplasm of cardiomyocytes and easily leaks to the circulation from damaged myocardium^[6-8]. H-FABP is a potential myocardial damage marker. We and others reported that elevated serum H-FABP levels can predict poor outcomes in patients with CHF^[9,10]. Progression of CHF is associated with persistent loss of cardiomyocytes, which can be clinically detected as a continuous increase in serum H-FABP levels^[11].

Electrocardiography (ECG) is routinely performed and is useful for evaluating the etiology of heart failure. Several electrocardiographic parameters were reported to predict poor outcome in HF patients^[12-14]. QRS prolongation indicated electrical disturbance and is associated with left ventricular dyssynchrony and poor cardiac prognosis in patients with CHF^[15-17]. Not

surprisingly, due to the complex pathogenesis of CHF, a single biomarker cannot be used to predict the absolute risk of future cardiac events. Therefore, the purpose of the present study was to investigate whether a combined measurement of a myocardial damage marker and electrical disturbance can be used to risk-stratify CHF patients.

MATERIALS AND METHODS

Study population

We prospectively studied 322 patients with CHF, who were admitted to our hospital for the diagnosis or treatment of CHF. The diagnosis of CHF was made by two cardiologists who used the generally accepted Framingham criteria, including a history of dyspnea and symptomatic exercise intolerance, signs of pulmonary congestion, peripheral edema, and radiologic or echocardiographic evidence of left ventricular enlargement or dysfunction. Demographic and clinical data including age, gender, New York Heart Association (NYHA) functional class, and medications at discharge were obtained from hospital medical records and interviews with patients. The diagnoses of hypertension, diabetes mellitus and hyperlipidemia were ascertained from the medical records or current or previous medical therapy. Glomerular filtration rate (GFR) was estimated using the modification of diet in renal disease equation with the Japanese coefficient, as previously reported^[18]. The exclusion criteria for the present study were acute coronary syndrome, bundle branch block, pace maker implantation, a serum creatinine concentration > 2.0 mg/dL, and implantation of a heart valve prosthesis.

Electrocardiographic and echocardiographic studies

Standard 12-lead ECG was performed at admission. QRS duration was measured by averaging of all heartbeats all leads. A normal QRS duration was defined as less than 120 ms and a prolonged QRS as 120 ms or longer. Transthoracic echocardiography was performed by physicians who were blinded to the biochemical data.

Assay of H-FABP and brain natriuretic peptide concentrations

Venous blood samples were obtained at admission for measurements of serum H-FABP levels. These samples were immediately centrifuged at 2500 G for 15 min at 4 °C. The clarified serum samples were frozen, stored at -70 °C, and thawed just before assay. H-FABP concentration was measured using a two-step sandwich enzyme-linked immunosorbent assay kit (MARKIT-M HFABP, Dainippon Pharmaceutical Co Ltd, Tokyo, Japan) as previously reported^[19,20]. The cut-off value for H-FABP concentration (4.5 ng/mL) was determined from a previous study^[21]. The same blood samples were used for measurement of plasma brain natriuretic peptide (BNP) concentrations. The samples were transferred to chilled tubes containing of ethylene diamine tetraacetic acid disodium salt (4.5 mg) and aprotinin (500 U/mL),

and immediately centrifuged at 1000 G for 15 min at 4 °C. The clarified plasma samples were frozen, stored at -70 °C and thawed just before assay. BNP concentrations were measured using a commercially available specific radioimmunoassay for human BNP (Shiono RIA BNP assay kit, Shionogi Co Ltd, Tokyo, Japan). The analytical ranges, and intra- and inter-assay coefficients of variation for the H-FABP and BNP assays were, 1.1-250 ng/mL, 3% and 3.5%, and 4.0-2000 pg/mL, 10.9% and 10.6%, respectively.

End points and follow-up

Patients were prospectively followed for a median period of 534 d (range 203-1014). Patients were followed in our hospital outpatient clinic every month. The other patients were followed by telephone twice a year until 2555 d after discharge. The end points were cardiac death, defined as death due to progressive heart failure, myocardial infarction or sudden cardiac death, and progressive heart failure requiring rehospitalization. Sudden cardiac death was defined as death without definite premonitory symptoms or signs, and was established by the attending physician. The study was approved by the Institutional Ethics Committee, and all patients gave written informed consent prior to participating. The study was performed in accordance with the Helsinki Declaration.

Statistical analysis

Results are presented as the mean values \pm SD for continuous variables and as percentages of the total number of patients for categorical variables. The independent samples *t* test and χ^2 test or linear regression analysis were used for comparison of continuous and categorical variables, respectively. A Cox proportional hazard analysis was performed to assess the independent predictors for cardiac events in the entire population. Statistical significance was defined as $P < 0.05$. Variables identified as significant by univariate analysis were entered into the multivariate analysis. The cardiac event-free curve was computed according to the Kaplan-Meier method, and comparison of cardiac event-free survival between subgroups was performed using the log-rank test. Receiver operating characteristic (ROC) curve analysis, as well as area under the curve (AUC) was used as measures of the predictive accuracy of traditional prognostic factors for cardiac events. In addition, the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated in order to quantify the improvement for the corrected reclassification and sensitivity after inclusion of high H-FABP levels and QRS prolongation in the model. Statistical analyses were performed using a standard software package (JMP version 8; SAS Institute Inc., Cary, NC, United States) or R 3.0.2 with additional packages (Rcmdr, Epi, pROC and PredictABEL).

RESULTS

Patient characteristics

Table 1 shows that clinical characteristics of the study patients. The mean age of the patients was 69 ± 13 years. There were 175 patients in NYHA functional class II, 105 in NYHA class III, and 42 in NYHA class IV. Diabetes mellitus, dyslipidemia, and hypertension were identified in 117 (36%), 87 (26%), and 217 (67%) of the CHF patients, respectively. The etiology of heart failure was dilated cardiomyopathy in 80 (25%) patients, hypertensive heart disease in 14 (4%), hypertrophic cardiomyopathy in 21 (7%), ischemic heart disease in 65 (20%), valvular heart disease in 80 (25%), arrhythmia in 24 (7%), and other etiologies in 38 (12%) patients. The median H-FABP and BNP levels were 4.7 (3.3-7.6) ng/mL and 397 (135-853) pg/mL, respectively. The mean QRS duration was 107 ± 20 ms and 61 patients (19%) showed QRS prolongation. Simple linear regression analysis showed that QRS duration was not correlated with H-FABP level ($r = 0.091$, $P = 0.1019$) or BNP level ($r = 0.066$, $P = 0.2356$) as shown in Figure 1.

Clinical outcomes

During the follow-up period, there were 117 primary events, including 27 cardiac deaths and 90 re-admissions for worsening CHF. Among 27 cardiac deaths, there were 21 deaths from worsening CHF, 2 fatal acute myocardial infarction, and 4 sudden cardiac deaths. The patients with cardiac events were older and had a more severe NYHA functional class compared to those who did not (Table 1). Furthermore, higher BNP and H-FABP levels, and a higher prevalence of QRS prolongation were observed in patients who experienced cardiac events, compared with those who did not. Patients who experienced cardiac events also had a lower estimated GFR (eGFR) compared with those who did not. There was no difference in gender, prevalence of atrial fibrillation, hypertension, diabetes mellitus or hyperlipidemia between CHF patients with and without cardiac events. Patients who experienced cardiac events took loop diuretics more frequently than patients who were event-free.

Independent predictors of cardiac events

To investigate the risk factors for cardiac events, Cox proportional hazards regression analyses were performed (Table 2). In the univariate analysis, high H-FABP levels and QRS prolongation were significantly associated with cardiac events. Further, age, NYHA functional class, BNP levels, and eGFR were significantly associated with cardiac events. In the multivariate analysis, NYHA functional class, eGFR, high serum H-FABP levels, and prolonged QRS duration were independently associated with cardiac events.

Table 1 Comparison of the clinical characteristics of patients with and without cardiac events

	All patients (<i>n</i> = 322)	Event-free (<i>n</i> = 205)	Cardiac event (<i>n</i> = 117)	<i>P</i> value
Age, yr	69 ± 13	67 ± 14	72 ± 11	0.0041
Female, <i>n</i> (%)	140 (43)	92 (45)	48 (41)	0.5024
NYHA functional class, II/III/IV	175/105/42	125/53/27	50/52/15	0.002
Etiology, <i>n</i> (%)				0.5273
Dilated cardiomyopathy	80 (25)	56 (27)	24 (21)	
Hypertensive heart disease	14 (4)	10 (5)	4 (3)	
Hypertrophic cardiomyopathy	21 (7)	15 (7)	6 (5)	
Ischemic heart disease	65 (20)	36 (18)	29 (25)	
Valvular heart disease	80 (25)	52 (25)	28 (24)	
Arrhythmia	24 (7)	14 (7)	10 (8)	
Others	38 (12)	22 (11)	16 (14)	
Atrial fibrillation, <i>n</i> (%)	109 (34)	64 (31)	45 (38)	0.1866
Diabetes mellitus, <i>n</i> (%)	117 (36)	71 (35)	44 (38)	0.5923
Dyslipidemia, <i>n</i> (%)	87 (26)	56 (26)	31 (27)	0.8732
Hypertension, <i>n</i> (%)	217 (67)	137 (67)	80 (68)	0.7758
Blood biomarkers				
BNP, pg/mL (IQR)	397 (135-853)	314 (101-710)	625 (280-1147)	0.0326
H-FABP, ng/mL (IQR)	4.7 (3.3-7.6)	4.0 (2.9-6.3)	6.0 (4.2-10.0)	< 0.0001
eGFR, mL/min per 1.73 m ²	65 ± 22	69 ± 23	58 ± 19	< 0.0001
Echocardiographic data				
LV end-diastolic diameter, mm	55 ± 10	54 ± 9	55 ± 12	0.6018
LV ejection fraction, %	49 ± 18	50 ± 18	47 ± 18	0.1472
Electrocardiogram				
Heart rate, beat/min	77 ± 22	78 ± 21	74 ± 19	0.0841
QRS duration, ms	107 ± 20	106 ± 18	109 ± 22	0.0989
QRS prolongation, <i>n</i> (%)	61 (19)	28 (17)	33 (28)	0.0014
Medications, <i>n</i> (%)				
ACE inhibitors and/or ARBs, <i>n</i> (%)	213 (66)	138 (67)	75 (64)	0.5577
β-blockers, <i>n</i> (%)	170 (53)	106 (52)	64 (55)	0.6048
Ca channel blockers, <i>n</i> (%)	66 (21)	41 (21)	25 (20)	0.77
Diuretics, <i>n</i> (%)	202 (63)	111 (54)	91 (78)	< 0.0001
Statins, <i>n</i> (%)	83 (26)	54 (26)	29 (25)	0.759

Data are presented as mean ± SD or % unless otherwise indicated. ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; BNP: Brain natriuretic peptide; eGFR: Estimated glomerular filtration rate; H-FABP: Heart-type fatty acid-binding protein; LV: Left ventricular; NYHA: New York Heart Association.

Table 2 Univariate and multivariate analyses for cardiovascular events

	HR	95%CI	<i>P</i> value
Univariate analysis			
Age, per 10-yr increase	1.297	1.105-1.524	0.0016
Female gender	0.829	0.573-1.199	0.3183
NYHA functional class II and III vs IV	1.960	1.381-2.747	0.0003
Atrial fibrillation	1.256	0.865-1.824	0.2304
Diabetes mellitus	1.103	0.758-1.605	0.6062
Dyslipidemia	0.958	0.635-1.447	0.8417
Hypertension	0.986	0.667-1.457	0.9459
BNP, per 1SD increase	1.166	1.019-1.334	0.0249
eGFR, per 1SD increase	0.589	0.467-0.733	< 0.0001
LV end-diastolic diameter, per 1SD increase	1.062	0.877-1.280	0.5272
LV ejection fraction, per 1SD increase	0.881	0.734-1.074	0.1998
Heart rate, per 1SD increase	0.869	0.724-1.062	0.1724
High H-FABP (> 4.5 ng/mL)	2.994	1.996-4.504	< 0.0001
QRS prolongation (≥ 120 ms)	1.897	1.264-2.832	0.0019
Multivariate analysis			
Age, per 10-yr increase	1.093	0.921-1.298	0.3055
NYHA functional class II and III vs IV	1.55	1.055-2.309	0.0262
BNP, per 1SD increase	0.948	0.811-1.151	0.7003
eGFR, per 1SD increase	0.733	0.571-0.938	0.0144
High H-FABP (> 4.5 ng/mL)	1.745	1.088-2.793	0.0210
QRS prolongation (≥ 120 ms)	1.612	1.060-2.451	0.0258

HR: Hazard ratio; SD: Standard deviation; BNP: Brain natriuretic peptide; eGFR: Estimated glomerular filtration rate; NYHA: New York Heart Association.

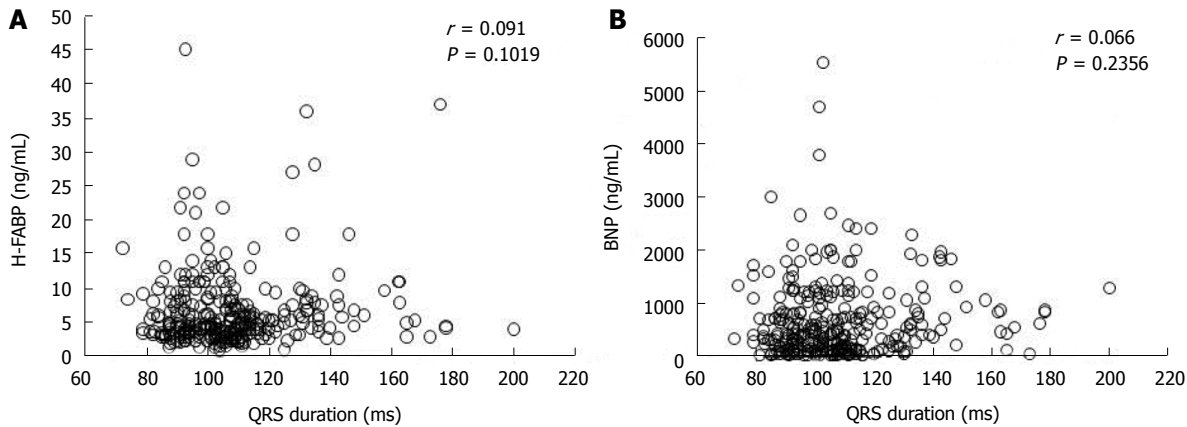


Figure 1 Relationship between QRS duration and heart-type fatty acid binding protein levels (A) and brain natriuretic protein levels (B). BNP: Brain natriuretic peptide; H-FABP: Heart-type fatty acid-binding protein.

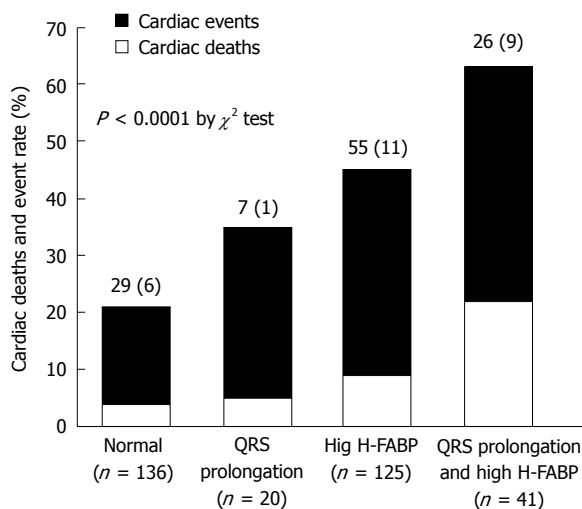


Figure 2 Cardiac mortality and all cardiac events among the four groups based on heart-type fatty acid-binding protein level and QRS duration. Normal group ($n = 136$), H-FABP ≤ 4.5 ng/mL and QRS duration < 120 ms; QRS prolongation group ($n = 20$), H-FABP ≤ 4.5 ng/mL and QRS duration ≥ 120 ms; high H-FABP group ($n = 125$), H-FABP > 4.5 ng/mL and QRS duration < 120 ms; and high H-FABP + QRS prolongation group ($n = 41$), H-FABP > 4.5 ng/mL and QRS duration ≥ 120 ms. H-FABP: Heart-type fatty acid-binding protein.

A combined assessment of QRS duration and H-FABP level

Simple linear analysis demonstrated that QRS duration was not correlated with H-FABP or BNP levels in patients with CHF (Figure 1). The patients were divided into four groups based on QRS prolongation and H-FABP cutoff values as shown in Figure 2: (1) normal group ($n = 136$), H-FABP ≤ 4.5 ng/mL, QRS duration < 120 ms; (2) QRS prolongation group ($n = 20$), H-FABP ≤ 4.5 ng/mL, QRS ≥ 120 ms; (3) high H-FABP group ($n = 125$), H-FABP > 4.5 ng/mL, QRS duration < 120 ms; and (4) high H-FABP + QRS prolongation group ($n = 41$), H-FABP > 4.5 ng/mL, QRS duration ≥ 120 ms. High serum H-FABP + QRS prolongation group showed the highest rates of cardiac deaths and cardiac events ($P < 0.001$). Multivariate Cox hazard analysis revealed that after

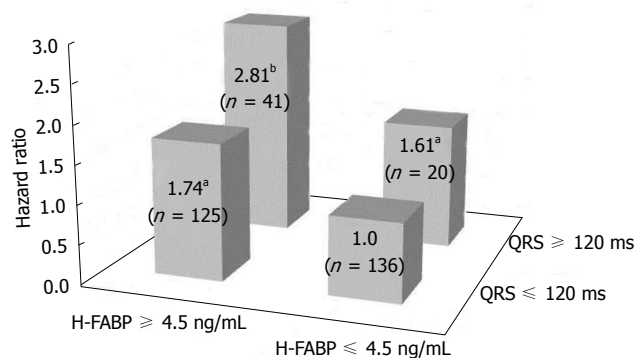


Figure 3 Hazard ratios relative to the normal group after adjustment for age, New York Heart Association functional class, brain natriuretic peptide level and estimated glomerular filtration rate. ^a $P < 0.05$, ^b $P < 0.01$ vs normal group. H-FABP: Heart-type fatty acid-binding protein.

adjustment for age, NYHA functional class, BNP levels and eGFR, the QRS prolongation, high H-FABP, and high H-FABP + QRS prolongation groups had 1.61-fold ($P < 0.05$), 1.74-fold ($P < 0.05$), and 2.81-fold higher risks of cardiac events ($P < 0.01$), respectively, compared with the normal group (Figure 3). The characteristics of these four groups are presented in Table 3. The QRS prolongation group had lower BNP levels than the high H-FABP and high H-FABP + QRS prolongation groups. The QRS prolongation group also had the lowest left ventricular (LV) ejection fraction and largest LV end-diastolic diameter among 4 groups. Kaplan-Meier analysis demonstrated that the high H-FABP + QRS prolongation group had a significantly higher rate of cardiac events than the other groups (Figure 4). In order to examine whether model fit and discrimination improved with the addition of high H-FABP levels and QRS prolongation to the traditional prognostic factors of age, BNP level, NYHA functional class and eGFR, the differences in area under the ROC curves, and the improvement in NRI and IDI were evaluated for two models: With (group 2) or without (group 1) a high H-FABP level and QRS prolongation. The area under the ROC curve for predicted cardiac events was significantly

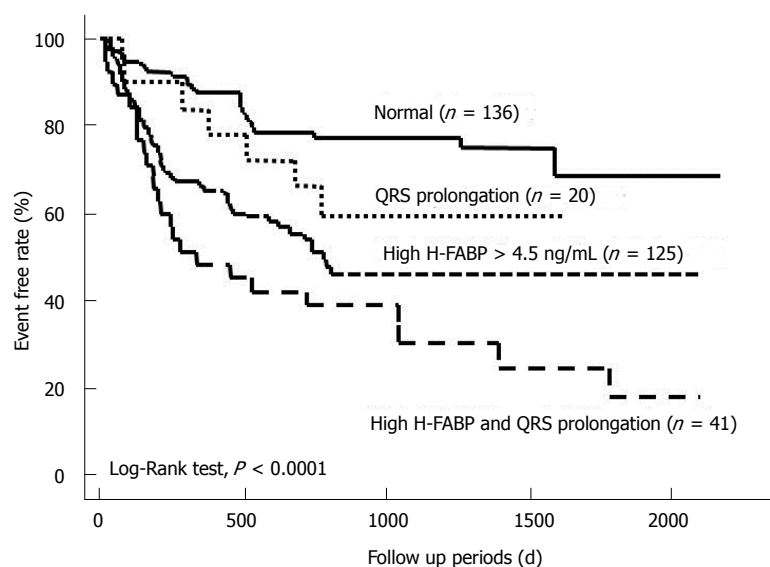


Figure 4 Kaplan-Meier analysis of the cardiac event-free curve in patients with chronic heart failure, who were stratified into four groups based on QRS duration and heart-type fatty acid-binding protein level. H-FABP: Heart-type fatty acid-binding protein.

Table 3 Clinical characteristics of the 4 subgroups of chronic heart failure patients

	Normal (<i>n</i> = 136)	QRS prolongation (<i>n</i> = 20)	High H-FABP (<i>n</i> = 125)	High H-FABP and QRS prolongation (<i>n</i> = 41)
Age, yr	65 ± 13	59 ± 11	74 ± 11 ^{a,b}	71 ± 13 ^b
Female, <i>n</i> (%)	58 (42)	10 (50)	55 (45)	17 (41)
NYHA functional class, II/III/IV	97/30/9	3/4/2013	51/54/20	14/18/9 ^c
Etiology, <i>n</i> (%)				
Dilated cardiomyopathy	33 (24)	8 (40)	24 (19)	15 (37)
Hypertensive heart disease	8 (6)	1 (5)	5 (4)	1 (2)
Hypertrophic cardiomyopathy	11 (8)	3 (15)	6 (5)	0 (0)
Ischemic heart disease	21 (15)	3 (15)	31 (24)	10 (24)
Valvular heart disease	40 (30)	3 (15)	29 (24)	8 (20)
Arrhythmia	12 (9)	0 (0)	8 (7)	4 (10)
Others	11 (8)	2 (10)	22 (17)	3 (7)
Atrial fibrillation, <i>n</i> (%)	48 (35)	7 (35)	41 (33)	13 (32)
Diabetes mellitus, <i>n</i> (%)	46 (33)	6 (28)	46 (37)	17 (41)
Dyslipidemia, <i>n</i> (%)	39 (28)	4 (20)	32 (26)	12 (29)
Hypertension, <i>n</i> (%)	92 (67)	11 (55)	89 (72)	25 (61)
Blood biomarkers				
BNP, pg/mL (IQR)	347 (69-453)	389 (213-855)	700 (311-1257) ^a	628 (328-1075) ^a
H-FABP, ng/mL (IQR)	3.2 (2.4-3.9)	3.6 (2.8-4.2)	7.6 (5.7-11.0) ^{a,b}	7.6 (5.7-9.8) ^{a,b}
eGFR, mL/min per 1.73 m ²	75 ± 20	71 ± 26	57 ± 20 ^a	52 ± 17 ^{a,d}
Echocardiographic data				
LV end-diastolic diameter, mm	52 ± 10	65 ± 9 ^{a,d}	54 ± 9 ^b	60 ± 10 ^{a,c}
LV ejection fraction, %	55 ± 18	35 ± 15 ^a	49 ± 17 ^b	38 ± 14 ^{a,d}
Electrocardiogram				
Heart rate, beat/min	78 ± 19	72 ± 13	79 ± 22	72 ± 20
QRS duration, ms	100 ± 10	143 ± 23 ^{a,d}	100 ± 10	138 ± 14 ^{a,d}
Medications, <i>n</i> (%)				
ACE inhibitors and/or ARBs, <i>n</i> (%)	86 (62)	13 (65)	85 (69)	29 (71)
β-blockers, <i>n</i> (%)	65 (47)	15 (75)	64 (52)	26 (63)
Ca channel blockers, <i>n</i> (%)	36 (26)	0 (0)	24 (20)	6 (15)
Diuretics, <i>n</i> (%)	72 (52)	14 (70)	82 (67)	34 (83) ^e
Statins, <i>n</i> (%)	40 (29)	5 (25)	28 (23)	10 (24)

^a*P* < 0.01 vs normal; ^b*P* < 0.01 vs QRS prolongation; and ^c*P* < 0.05 and ^d*P* < 0.01 vs High H-FABP by analysis of variance with the Scheffe post hoc test. ^e*P* < 0.01 by χ^2 test. Normal group (*n* = 136): H-FABP ≤ 4.5 ng/mL and QRS duration < 120 ms, QRS prolongation group (*n* = 20): H-FABP ≤ 4.5 ng/mL and QRS duration ≥ 120 ms, High H-FABP group (*n* = 123): H-FABP > 4.5 ng/mL and QRS duration < 120 ms, and High H-FABP and QRS prolongation group (*n* = 41): H-FABP > 4.5 ng/mL and QRS duration ≥ 120 ms. ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; BNP: Brain natriuretic peptide; eGFR: Estimated glomerular filtration rate; H-FABP: Heart-type fatty acid-binding protein; LV: Left ventricular; NYHA: New York Heart Association.

Table 4 Statistics for model fit and improvement with the addition of high heart-type fatty acid-binding protein and QRS prolongation predicted on the prediction of cardiac events

	Group 1	Group 2	P value
AUC of ROC curve	0.668	0.706	0.029
NRI (95%CI)	Ref	0.223 (0.073-0.372)	0.003
IDI (95%CI)	Ref	0.036 (0.015-0.056)	0.016

AUC: Area under the curve; CI: Confidence interval; IDI: Integrated discrimination improvement; NRI: Net reclassification improvement; ROC: Receiver operator characteristics. Group 1: Age + BNP + NYHA + eGFR; Group 2: Group 1 + H-FABP > 4.5 ng/mL + QRS duration \geq 120 ms. BNP: Brain natriuretic peptide; eGFR: Estimated glomerular filtration rate; H-FABP: Heart-type fatty acid-binding protein; NYHA: New York Heart Association.

greater for group 2 than group 1 (Table 4). Further, the group 2 model improved the NRI and IDI values for predicting cardiac events compared with the group 1 model.

DISCUSSION

In the present study, we demonstrated that QRS prolongation as a marker of electrical disturbance, and high H-FABP levels as a marker of ongoing myocardial damage are significantly related to cardiac events in CHF patients. The inclusion of high H-FABP level and QRS prolongation with BNP level, NYHA functional class and eGFR in the model for predicting cardiac events improved the NRI and IDI values, indicating effective reclassification and discrimination. Therefore, a combined measurement of H-FABP levels and QRS duration is a promising strategy for risk stratification for future cardiac events in CHF patients.

There are several markers of myocardial damage, including troponin T, troponin I and H-FABP^[9,22]. Since H-FABP is a small cytosolic protein, it is readily released into the circulation when cardiomyocytes are injured. The mechanism by which serum levels of H-FABP are increased in CHF has been reported to be related to cardiomyocyte necrosis, apoptosis, chronic inflammation and microcirculatory disorder^[8,23]. In this study, elevated levels of H-FABP were significantly associated with cardiac events, which are consistent with previous reports^[19,24].

QRS duration reflects LV conduction disturbance, LV systolic dysfunction and LV dilation^[25]. In this study, the QRS prolongation group had the lowest LV ejection fraction and the greatest LV end-diastolic diameter compared with the other groups. Since left bundle branch block is an unfavorable prognostic marker in CHF patients^[26,27], patients with bundle branch block were excluded from the present study. Therefore, QRS prolongation is an independent risk factor for cardiac events in patients with CHF, irrespective of bundle branch block. Recently, it was reported that cardiac resynchronization therapy (CRT) can improve the cardiac prognosis in patients with QRS prolongation^[28,29] and

measurement of QRS duration has attracted widespread interest.

The present study showed that there was no correlation between QRS duration and H-FABP or BNP levels in patients with CHF. These results suggest that H-FABP and BNP levels and QRS duration reflect different pathophysiological backgrounds. In the multivariate analysis, high H-FABP levels and QRS prolongation were independent predictors of cardiac events. In addition, multivariate Cox hazard analysis revealed that the combination of elevated H-FABP levels and QRS prolongation was associated with the highest increase in risk for cardiac events (2.81-fold) compared with the normal group.

Taniguchi *et al.*^[30] reported that the combined measurement of BNP levels and QRS duration can be used to predict cardiac events in heart failure patients. We recently determined that the AUC for prediction of cardiac events in heart failure was greater for H-FABP level than for BNP level^[10]. Both the sensitivity and the specificity for predicting cardiac events were significantly greater for H-FABP level than for BNP level, indicating that H-FABP level is superior to BNP level for predicting cardiac events in CHF patients^[10]. In this study, BNP level was not associated with cardiac events in the multivariate analysis. A weak correlation between H-FABP levels and BNP levels was observed (data not shown), which was consistent with the results from a previous study^[10]. H-FABP and BNP reflect different pathophysiological backgrounds as markers of left ventricular overload. Combined assessment of H-FABP as a biochemical marker of myocardial damage and QRS prolongation as an electrophysiological marker of myocardial impairment is a potentially useful method for risk-stratification in CHF patients.

This study has several limitations. The effect of changes in QRS duration and H-FABP level between the time of hospitalization and discharge were not evaluated. However, it was reported that QRS duration in patients with CHF did not change significantly over two years^[31]. On the other hand, although H-FABP level is usually decreased at discharge, persistently elevated H-FABP levels were reported to be associated with adverse outcomes in patients with CHF^[32]. Therefore, further research is needed to elucidate whether the combined assessment of H-FABP level at discharge and QRS prolongation can be used to more precisely predict the cardiac prognosis of patients with CHF.

In conclusion, the combined assessment of markers of ongoing myocardial damage and electrical disturbance can be used to risk-stratify patients with CHF.

ACKNOWLEDGMENTS

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COMMENTS

Background

Despite advancing medical therapy, chronic heart failure (CHF) is a major health problem with high morbidity and mortality. It is important to risk-stratify patients with CHF.

Research frontiers

Prolonged QRS duration reflects intraventricular conduction disturbance caused by left ventricular fibrosis and cardiac myocyte loss, and is associated with cardiac prognosis in patients with CHF. However, there are CHF patients with narrow QRS duration showing poor prognosis. Biochemical myocardial damage markers are also useful for predicting prognosis in addition to electrophysiological myocardial impairment markers in CHF patients.

Innovations and breakthroughs

The combined assessment of markers of ongoing myocardial damage and electrical disturbance can risk-stratify patients with CHF.

Applications

It may be difficult to predict prognosis of CHF patients using a single biomarker precisely. The combined assessment of commonly used biomarkers is easily applicable to clinical practice.

Terminology

Since heart-type fatty acid binding protein (H-FABP) is a low molecular weight protein and abundant in the cytosolic fraction of cardiomyocytes, it is rapidly released into the circulation from damaged myocardium. Therefore, H-FABP is a potential marker of ongoing myocardial damage.

Peer-review

The manuscript was very easy to follow and well written.

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Cough induced syncope: A hint to cardiac tamponade diagnosis

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lung adenocarcinoma who presented with shortness of breath and frequent episodes of cough-induced syncope. A large pericardial effusion was found on echocardiogram suggestive of cardiac tamponade. Pericardiocentesis was done which improved the dyspnea and eventually resolved the syncope. There are only two other cases reported in the literature with cough-induced syncope in the setting of pericardial effusion or cardiac tamponade. Our clinical vignette also highlights the importance of pulsus paradoxus identification in patients with cough induced syncope to rule out cardiac tamponade since this is the most sensitive physical finding for its diagnosis.

Key words: Cardiac tamponade; Cough-induced syncope; Pericardial effusion

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Core tip: Cough-induced syncope should be a hint towards the consideration of either pericardial effusion or cardiac tamponade. Aside from the medical history and the diagnostic imaging modalities to include echocardiogram and chest computed tomography, clinical evaluation to explore pulsus paradoxus is imperative which has a high sensitivity in the diagnosis of cardiac tamponade. Timely diagnosis of cardiac tamponade because of these clues translate into prompt intervention to prevent the deleterious complications associated with it.

Ramirez R, Lasam G. Cough induced syncope: A hint to cardiac tamponade diagnosis. *World J Cardiol* 2017; 9(5): 466-469 Available from: URL: <http://www.wjgnet.com/1949-8462/full/v9/i5/466.htm> DOI: <http://dx.doi.org/10.4330/wjc.v9.i5.466>

Abstract

We report a case of a 75-year-old male with history of

INTRODUCTION

Cough-induced syncope is a validated rare phenomenon

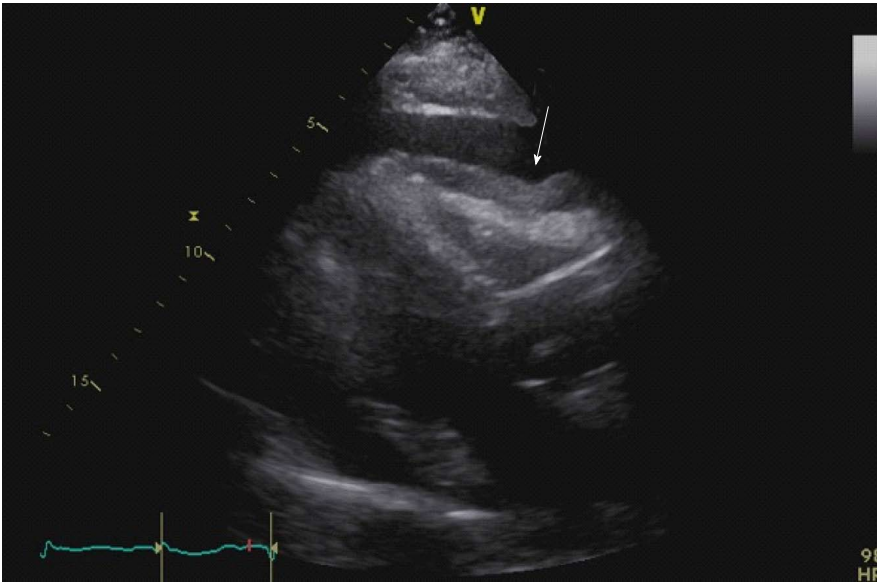


Figure 1 Transthoracic echocardiogram showing a large pericardial effusion with right ventricular diastolic indentation and collapse suggestive of tamponade.

which denotes cough as the etiology of the syncope and has been linked with chronic obstructive disease and constrictive pericarditis. It is very rare to have cough-induced syncope in a case of pericardial effusion or cardiac tamponade with only two other reported cases in the literature. Therefore, we describe a case of cough-induced syncope in an elderly gentleman with cardiac tamponade, elaborating further the pathophysiology behind this rare occurrence.

CASE REPORT

A 75 years old male with known history of stage 4 adenocarcinoma of the lung with recent right lung biopsy, chronic obstructive pulmonary disease, hypertension, diabetes mellitus, hyperlipidemia and peripheral vascular disease presented with symptoms of increased shortness of breath for several days before hospitalization accompanied by cough with subsequent syncopal episodes. He had three syncopal episodes, two of them witnessed and were associated with coughing spells, lasting for 30 s to 1 min with complete recovery thereafter. No seizure-like activity was noted during the syncopal event. Prior to this presentation, he had never had a syncopal episode. The patient's syncope was not associated with other precipitants including laughter and micturition. On admission to the hospital, he was hypertensive with a blood pressure of 151/88 mmHg and with a pulse rate of 100. General appearance was apparent for occasional cough with no signs of cyanosis nor worsening shortness of breath. Further examination revealed mild diminished breath sounds at the bases. Cardiac evaluation showed sinus tachycardia with a soft 2/6 systolic murmur at the apex and a pulsus paradoxus of 16 mmHg but no note of muffled heart sounds, distended neck veins or peripheral edema.

Neuroexamination was intact and nonfocal. Pericardial effusion was considered immediately on admission because of his medical history, his symptoms, and the pulsus paradoxus which was confirmed later on by imaging studies. Hemogram revealed mild anemia (12.5 g/dL) and leukocytosis (12.8/nL). Electrocardiogram demonstrated sinus tachycardia (103 bpm) with intra-ventricular conduction delay but no low voltage complexes. No evident electrical alternans appreciated. Carotid ultrasound was done during his hospitalization which demonstrated no evidence of hemodynamically significant stenosis of the carotid system bilaterally and with normal antegrade flow of the vertebral arteries. Chest radiograph showed right pleural effusion. Chest computed tomography confirmed worsening bilateral pleural effusion as well as pericardial effusion but with no pulmonary embolus. Transthoracic echocardiography revealed a large pericardial effusion with right ventricular diastolic indentation and collapse suggestive of tamponade (Figure 1) which was also evident on the M-mode (Figure 2). Mitral valve inflow E wave velocity showed greater than 25% respiratory variation also suggestive of tamponade physiology (Figure 3). The cardiothoracic surgery team was involved to move forward with a pericardial window. Pericardiocentesis was done and drained 600 mL of hemorrhagic fluid. Subsequently, thoracentesis was performed and drained 500 mL of serosanguineous pleural fluid. Pericardial and pleural fluid cytology revealed adenocarcinoma. After drainage of both pericardial and pleural effusion, his dyspnea improved significantly and subsequently his cough-induced syncope resolved.

DISCUSSION

Cough-induced syncope is a well-recognized but uncommon

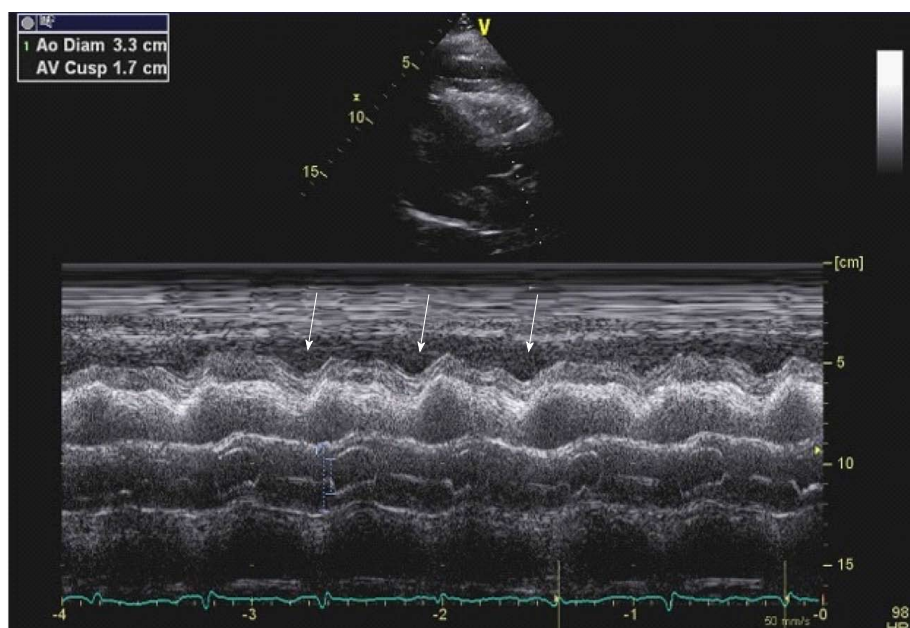


Figure 2 M-mode showing right ventricular diastolic indentation.

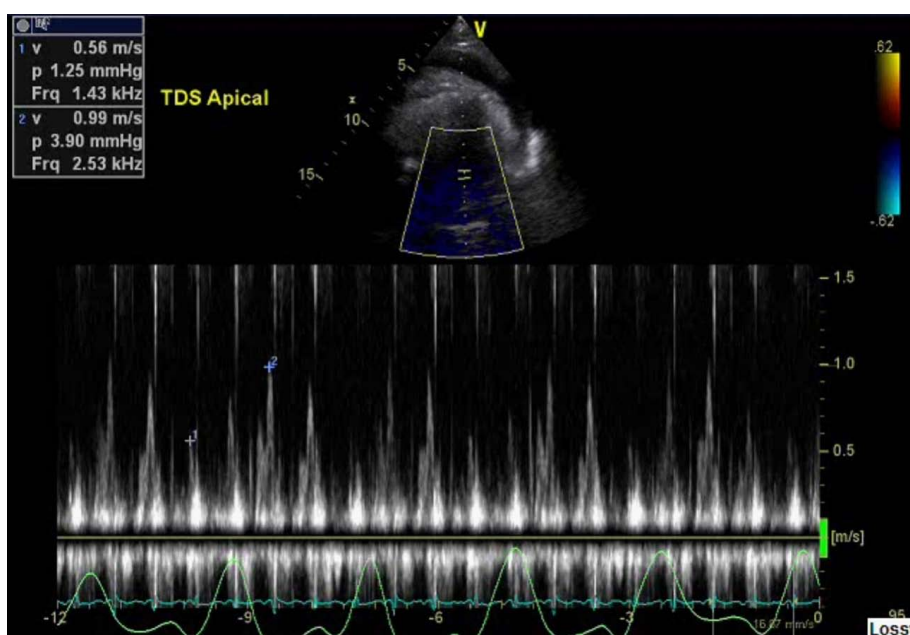


Figure 3 Transthoracic echocardiogram showing a mitral valve inflow E wave velocity greater than 25% respiratory variation suggestive of tamponade physiology.

mon phenomenon in which the cough is the main culprit of the syncope^[1]. It is associated with chronic obstructive pulmonary disease and constrictive pericarditis^[2], although it is very rare to have cough induced syncope in a case of pericardial effusion or cardiac tamponade^[3]. The proposed pathophysiology is multifactorial wherein there is a more exaggerated drop in blood pressure in response to cough compared to patients with other causes of syncope^[4]. Also, the cough increases intra-thoracic pressure, which decreases blood return to the heart and cardiac output, which is already reduced by the cardiac tamponade or moderate/large pericardial

effusion. This phenomenon has been reported with even small pericardial effusions^[5]. The combination of these events leads to cerebral hypoperfusion resulting to syncope. In subacute cardiac tamponade, these events occur over days to weeks and is usually associated with neoplastic, uremic or idiopathic pericarditis; it may be asymptomatic early in the course, but once intracardiac pressures reach a critical value, the patients develop symptoms of increased filling pressures and limited cardiac output and syncopal events^[6]. There are two reported cases in the literature of moderate pericardial effusion associated with cough-induced syncope which

also presented with pulsus paradoxus with a drop of > 15 mmHg systolic blood pressure but no evidence of echocardiographic criteria for tamponade^[1,3]. Pulsus paradoxus greater than 10 mmHg with a pericardial effusion increases the likelihood of tamponade (likelihood ratio, 3.3; 95%CI: 1.8-6.3), while a pulsus paradoxus of 10 mmHg or less lowers the likelihood (likelihood ratio, 0.03; 95%CI: 0.01-0.24)^[7]. Sensitivity of pulsus paradoxus for tamponade exceeds 80% and is higher than any other single physical finding although its specificity is only 70%^[8]. Echocardiogram's sensitivity is not significantly superior than clinical examination with reported sensitivity of the echocardiographic findings of right atrial collapse ranging from 50% to 100% and specificity ranging from 33% to 100%. Its sensitivity in identifying right ventricular collapse ranges from 48% to 100% whereas specificity ranges from 72% to 100%^[9,10]. In one of the reported cases of cough induced syncope, the pericardial effusion was from metastatic non-small cell carcinoma, while the other case was secondary to suspected viral pericarditis in which pericardiocentesis of both cases afforded complete resolution of cough-syncope syndrome cycle^[1,3].

It is important to consider either pericardial effusion or cardiac tamponade in any case of cough-induced syncope. Pulsus paradoxus has a high sensitivity in the diagnosis of cardiac tamponade and should therefore be checked in every patient with cough-induced syncope, consequently, can provide early diagnosis and intervention.

COMMENTS

Case characteristics

This is an interesting clinical vignette on syncope that was precipitated by cough which may serve as a clue to consider the diagnosis of pericardial effusion or cardiac tamponade.

Clinical diagnosis

The patient presented with progressive shortness of breath accompanied by cough with subsequent syncopal episodes, noted clinically to have pulsus paradoxus, and was found out to have a pericardial effusion with tamponade physiology on echocardiocardiogram.

Differential diagnosis

Cerebrovascular accident, vasovagal syncope, seizure.

Laboratory diagnosis

Pericardial and pleural fluid cytology revealed adenocarcinoma.

Imaging diagnosis

Chest computed tomography showed both pericardial effusion and bilateral pleural effusion but with no pulmonary embolus while transthoracic echo-

cardiography revealed a large pericardial effusion with tamponade.

Treatment

Surgical drainage of the pericardial and pleural fluid afforded significant improvement of dyspnea and resolution of cough-induced syncope.

Related reports

Cough-induced syncope is a very rare occurrence that has been associated with evolving pericardial effusion or cardiac tamponade with only two similar cases reported in the literature.

Term explanation

Pulsus paradoxus is a drop in systolic blood pressure of more than 10 mmHg during inspiration which is a sign of cardiac tamponade or pericarditis.

Experiences and lessons

Pericardial effusion or cardiac tamponade should be considered in patients with cough-induced syncope especially if accompanied by pulsus paradoxus which has a high sensitivity in such case.

Peer-review

The report has clinical interest.

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