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REVIEW

Lipoprotein abnormalities in South Asians and its association with cardiovascular disease: Current state and future directions

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Abstract

South Asians have a high prevalence of coronary heart disease (CHD) and suffer from early-onset CHD compared to other ethnic groups. Conventional risk factors may not fully explain this increased CHD risk in this population. Indeed, South Asians have a unique lipid profile which may predispose them to premature CHD. Dyslipidemia in this patient population seems to be an important contributor to the high incidence of coronary atherosclerosis. The dyslipidemia in South Asians is characterized by elevated levels of triglycerides, low levels of high-density lipoprotein (HDL) cholesterol, elevated lipoprotein(a) levels, and a higher atherogenic particle burden despite comparable low-density lipoprotein cholesterol levels compared with other ethnic subgroups. HDL particles also appear to be smaller, dysfunctional, and proatherogenic in South Asians. Despite the rapid expansion of the current literature with better understanding of the specific lipid abnormalities in this patient population, studies with adequate sample sizes are needed to assess the significance and contribution of a given lipid parameter on overall cardiovascular risk in this population. Specific management goals and treatment thresholds do not exist for South Asians because of paucity of data. Current treatment recommendations are mostly extrapolated from Western guidelines. Lastly, large, prospective studies with outcomes data are needed to assess cardiovascular benefit associated with various lipid-lowering therapies (including combination therapy) in this patient population.

Key words: Dyslipidemia; South Asians; Asian Indians; Cardiovascular disease

Core tip: South Asians have a high prevalence of coronary heart disease (CHD) and suffer from early-onset CHD. Indeed, an important contributor is their unique lipid profile which is characterized by elevated levels of triglycerides, low levels of high-density lipoprotein (HDL) cholesterol, elevated lipoprotein(a) levels, a higher atherogenic particle burden despite comparable low-density lipoprotein cholesterol levels compared with other ethnic subgroups. HDL particles also appear to be smaller, dysfunctional, and proatherogenic. Despite the rapid expansion of the current literature with better understanding of the specific lipid abnormalities in this patient population, specific management goals and treatment thresholds do not exist for South Asians because of paucity of data. Current treatment recommendations are mostly extrapolated from Western guidelines. Lastly, large, prospective studies with outcomes data are needed to assess cardiovascular benefit associated with various lipid-lowering therapies (including combination therapy) in this patient population.

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INTRODUCTION

The term "South Asian" refers to people who have ancestral origins in the Indian subcontinent (the countries of India, Pakistan, Bangladesh, Sri Lanka, and Nepal), where 1.6 billion people live. This region constitutes about 1/5 of the world's population. Nearly 3.6 million South Asians live in the United States, and the South Asian population has the highest rates of coronary heart disease (CHD) among all ethnic groups[1]. CHD in this population is usually premature and severe with 3- to 5-fold higher risk of morbidity and mortality[1-4]. The prevalence of CHD is higher in South Asian immigrants compared with the overall United States population, with similar rates among vegetarians and non-vegetarians[4-6]. Interheart, a global case-control study, was performed in 15152 cases with acute myocardial infarction (AMI) and 14820 controls in 52 countries. Of these, 1732 cases and 2204 controls were South Asian. Median age at first AMI was 53 years in South Asia compared with 63 years in both China and Western Europe. The highest proportions of cases with first AMI at age 40 years or younger were in men from the Middle East (12.6%), Africa (10.9%), and South Asia (9.7%), and the lowest proportions were in women from China and Hong Kong (1.2%), South America (1.0%), and central and eastern Europe (0.9%)[7]. These results indicate the magnitude of premature CHD risk in South Asians.

Although CHD rates in the general United States population have declined over the last few decades because of aggressive modification of risk factors and population-based interventions[8], the rates have conversely doubled in South Asian immigrants[3] and remain higher than their counterparts in their country of origin[9-11].

Given the consistent findings of increased prevalence, premature onset, and increased mortality from CHD in South Asians, there has been much interest in determining the underlying causes. Conventional risk factors such as hypertension, hypercholesterolemia, diabetes mellitus, abdominal obesity, metabolic syndrome, and tobacco use have been clearly associated with CHD risk among South Asian populations[7,12].

Other factors such as sedentary life style and dietary influences also play a role. Although a considerable percentage of South Asians are vegetarians, excess sugars and refined carbohydrates remain problematic for this population. Indeed India is among the largest consumers of sugar in the world. Diet rich in sugar and processed carbohydrates may be a considerable threat to the future health and wellness of the increasingly sedentary South Asian people with their innate genetic predisposition to CHD.

Although South Asians represent an heterogeneous population, with varied practices in terms of diet and exercise, they have a much higher prevalence of diabetes, insulin resistance, central obesity, increased thrombotic tendency, and physical inactivity than other populations[1,7,9,13-16]. Conversely, the prevalence of hypertension, smoking, and obesity (using traditional body mass index cut-offs) is lower in South Asians compared with the Western World[5]. Studies comparing South Asians with other ethnic groups have consistently shown that differences in these risk factors do not fully account for the excess incidence of CHD noted in South Asians[1,3,7,17-21]. The Study of Health Assessment and Risk in Ethnic Groups assessed conventional and novel cardiovascular risk factors among 985 participants of South Asian, Chinese, and European descent living in Canada. South Asians had an increased prevalence of glucose intolerance, higher total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglyceride levels, and lower high-density lipoprotein cholesterol (HDL-C) levels compared with Caucasians. These abnormalities only partially explained the high atherosclerosis burden (defined by carotid atherosclerosis measured with B-mode ultrasonography) in this population[14]. Thus, other factors may apply to the increased CHD risk in South Asians. Despite these findings, the INTERHEART study reported the association of smoking, history of hypertension or diabetes, waist/hip ratio, dietary patterns, physical activity, consumption of alcohol, blood apolipoproteins, and psychosocial factors with myocardial infarction in 9 ethnic populations including South Asians. Dyslipidemia appeared to be the strongest contributor of AMI in South Asians, with a population-

attributable risk of 49.2%[22]. Therefore, dyslipidemia appears to be an important determinant of increased CHD burden in South Asians.

In this article, we review the lipid and lipoprotein abnormalities in South Asian population as a potential cause of increased CHD risk. We also provide a succinct discussion on the efficacy of lipid-lowering therapy in South Asians. In Table 1, we provide references and a brief overview of studies discussed in this review. In Table 2, we summarize major lipid abnormalities in South Asians.

SEARCH STRATEGY

A PubMed/Medline search using key words "South Asian, Asian, Indian, lipids, cholesterol, cardiovascular disease, metabolic syndrome" was conducted. Studies since 1990 were included. Individual studies were initially screened using their titles and abstract content. An initial pool of studies was identified with this methodology. We subsequently reviewed references listed in the selected studies and included them in this review when relevant to the topic. Individual study references known to the authors of this review were also included.

DYSLIPIDEMIA IN SOUTH ASIANS

Total cholesterol, LDL-C and small dense LDL

Hypercholesterolemia (TC > 200 mg/dL) has been reported to have a prevalence of up to 35% in men and 36% in women from South Asian countries[23-25]. LDL-C is a well-established marker for the occurrence, recurrence, and severity of CHD. It is the co-primary target for lipid-lowering therapy as per the National Lipid Association recommendations for cholesterol management[26].

Elevated LDL-C levels clearly predict CHD risk in the South Asian population[17,22,27,28]. In various reports, LDL-C levels have been found to be either similar[5,29-32] or lower[33] among South Asians compared with Caucasians. Compared with Caucasian participants in the Framingham Offspring Study, LDL-C level and LDL particle size were similar in South Asians (LDL-C level: 139 ± 33 mg/dL *vs* 135 ± 31 mg/dL, respectively, $P < 0.10$; and LDL particle size: 20.6 nmol ± 0.7 *vs* 20.7 nmol ± 0.6, respectively, $P < 0.08$)[31]. LDL-C levels did not discriminate between Asian Indian and non-Asian Indian males[30]. On the other hand, studies have shown that CHD may appear at relatively lower LDL-C levels in South Asians. As shown in the INTERHEART study, although the overall associations between LDL-C and risk for AMI were similar among South Asians and others, South Asians had LDL-C levels that were on average 10 mg/dL lower than other groups. Interestingly, the proportion of cases and control subjects from Asia who had LDL-C levels < 100 mg/dL was 25.5% and 32.3% respectively, compared with 19.4% and 25.3% in non-Asians, with consistent results in both sexes[22]. These results indicate that although LDL-C is associated with AMI risk in South Asians, the risk is elevated even at a much lower LDL-C level compared with other ethnic groups.

Another study analyzed metabolic profile in 1066 Indian patients of whom 877 had CHD and 189 did not have CHD. The 50th percentile for TC was 205 mg/dL for the cases and 186 mg/dL for controls, while for triglycerides, the 50th percentile was 158 mg/dL for cases and 140 mg/dL for controls, thus suggesting the occurrence of CHD in this patient population at relatively lower levels of cholesterol[34].

Why South Asians carry a higher CHD risk at a given LDL-C level remains a question. One of the postulated mechanisms is that South Asians carry a higher LDL particle burden at a given LDL-C level. Smaller LDL particles are denser and may be more atherogenic[35]. A small study showed that the prevalence of small dense LDL, (defined as LDL subclasses 5 and 6 as measured by the Vertical Auto Profile test) was significantly higher in Asian Indians ($n = 39$) compared with white subjects ($n = 39$) (44% *vs* 21%, $P < 0.05$)[36]. A nonsignificant trend towards lower LDL particle size as measured by gel electrophoresis was also shown in South Asian adolescent boys compared with age-matched Caucasian adolescent boys[37]. Importantly, the INTERHEART study showed that for any LDL-C level, South Asians had higher apolipoprotein (apo) B concentration compared with other ethnic groups, indicating that for any LDL-C level, South Asians carry a higher number of atherogenic lipoproteins[22].

Therefore, although elevated LDL-C levels predict CHD risk in South Asians as in other ethnicities, the LDL-C levels in general are similar or lower in South Asians compared with other ethnicities. As shown in INTERHEART, a higher LDL-C level, although less frequent in South Asians, carries a similar risk for myocardial infarction as in other ethnic groups. In addition, at any given LDL-C level, South Asians tend to carry a higher total atherogenic burden as noted by higher levels of LDL particles and apo B in some studies as described above.

Triglycerides and HDL-C

HDL-C levels have been associated with a lower risk of CHD, and increasing HDL-C levels and augmenting HDL function have been associated with vascular protective effects[38-41]. Low HDL-C level (< 40 mg/dL) was defined as a CHD risk factor by the National Cholesterol Education Program Adult Treatment Panel Ⅲ guidelines[42]. Conversely, elevated triglycerides (> 150 mg/dL) are associated with increased CHD risk and are commonly associated with other lipid abnormalities (elevated non-HDL-C levels and increased LDL particle number) and nonlipid risk factors (diabetes mellitus and metabolic syndrome)[43].

One of the most common dyslipidemia in South Asians is low HDL-C and high triglycerides[14,23-25,44]. The rate of hypertriglyceridemia has shown to be higher in South Asians compared to Caucasians in several studies[45]. Hypertriglyceridemia (> 150 mg/dL) was observed in up to 70% of South Asian populations in studies with large

Table 1 Articles related to dyslipidemias in South Asians

Ref.	Methodology	Primary end point
Enas *et al*[5]	Cross-sectional, case-control study in Asian Indians and Caucasians (*n* = 1688)	CV risk factors
Anand *et al*[14]	Comparative population-based study in South Asians, Chinese, and Europeans (*n* = 985)	CV risk factors
Tillin *et al*[17]	Retrospective chart review (*n* = 2049 Europeans, 1517 South Asians, and 630 African Caribbeans)	CV risk factors
Karthikeyan *et al*[22]	Cross-sectional, population-based case-control study in 65 centers in Asia (*n* = 5731 cases of a first AMI *vs* 6459 controls)	CV risk factors
Gupta *et al*[23]	Cross-sectional study in South Asians (*n* = 1800)	CV risk factors
Sekhri *et al*[25]	Cross-sectional study in Indians (*n* = 10642 men and *n* = 1966 women)	CV risk factors
Hoogeveen *et al*[27]	Cross-sectional comparative study in Indians living in India (*n* = 103) *vs* those living in United States (*n* = 206)	Lipid profile
Sewdarsen *et al*[28]	Cross-sectional, case-control study in Indian men with CAD (*n* = 50) *vs* controls (*n* = 122)	Lipid profile
Lyratzopoulos *et al*[29]	Comparative study between South Asians and Caucasians (*n* = 34122 men and 37294 women)	CV risk factors
Superko *et al*[30]	Comparative study between Asian Indian men (*n* = 224) and non-Asian Indian men (*n* = 239)	Lipid profile
Bhalodkar *et al*[31]	Comparative study between Asian Indian men (*n* = 211) and Caucasian men (*n* = 1684)	Lipid profile
Joseph *et al*[32]	Descriptive study in Asian Indians (*n* = 206)	Lipid profile
Cappuccio *et al*[33]	Population-based survey in 505 South Asians, 524 Caucasians, and 549 Africans	CV risk factors
Krishnaswami *et al*[34]	Cross-sectional study in 1066 Indian male patients	Lipid profile
Kulkarni *et al*[36]	Cross-sectional study in 39 Asian Indians and 39 Caucasians	Lipid profile
Rashid *et al*[53]	Comparative study in 135 adolescent Indian and Caucasian boys	Lipid profile
Misra *et al*[45]	Comparative study in Asian Indians and Caucasians	CV risk factors
Bhardwaj *et al*[46]	Cross-sectional epidemiological descriptive study in 459 Indian subjects	CV risk factors
Gopinath *et al*[47]	Community-based epidemiological survey in 13414 Indian adults	CV risk factors
Misra *et al*[48]	Cross-sectional epidemiological descriptive study in 532 Indian subjects	CV risk factors
Ehtisham *et al*[50]	Cross-sectional community-based cohort study of 129 Caucasian European and Asian Indian boys	CV risk factors
Patel *et al*[51]	Cross-sectional comparative study in Indians (*n* = 294) and their immigrant counterparts in UK (*n* = 242)	Lipid profile
Sharobeem *et al*[52]	Cross-sectional study in South Asians with stroke (*n* = 55) and healthy controls (*n* = 85)	Lipid profile
Chow *et al*[54]	Cross-sectional comparative study in Indian (*n* = 303) and Caucasian (*n* = 1111) subjects	Association of CIMT with lipid profile
Dodani *et al*[55]	Cross-sectional study in South Asian immigrants in United States	Association of CIMT with lipid profile
Dodani *et al*[56]	Cross-sectional community-based study in 130 South Asian immigrants in United States	Association of CIMT with lipid profile
Isser *et al*[74]	Descriptive study in 50 Indian patients with premature CAD and their first-degree relatives	Lp(a) levels
Palaniappan *et al*[75]	Cross-sectional community-based study in Asian Indian American, African American, and Caucasian women (*n* = 70 each)	Lipid profile
Kamath *et al*[76]	Cross-sectional community-based study in 47 South Asian and 47 American women	CV risk factors
Anand *et al*[77]	Comparative cross-sectional study in South Asians and Americans	Lipid profile
Chopra *et al*[78]	Comparative study in 74 Indians with CAD and 53 controls	Lp(a) levels
Gambhir *et al*[79]	Comparative study in 50 Indians with CAD and 50 controls	Lp(a) levels
Gupta *et al*[80]	Descriptive study in 101 Indian subjects	Lp(a) levels
Articles related to treatment of dyslipidemias in South Asians		
Lee *et al*[89]	Rosuvastatin pharmacokinetics in White, Chinese, Malay, and Asian Indian subjects (*n* = 35 each)	
Patel *et al*[83]	Efficacy and safety of atorvastatin in 33 hyperlipidemic South Asians	
Gupta *et al*[85]	Lipid-modifying effects of atorvastatin and simvastatin in 86 South Asians and 137 Caucasians	
Gupta *et al*[84]	ACTFAST: 12 wk prospective, open-label study of atorvastatin in 1978	

AMI: Acute myocardial infarction; CAD: Coronary artery disease; ACTFAST: Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration; CIMT: Carotid intima-media thickness; Lp(a): Lipoprotein(a); CV: Cardiovascular.

sample sizes[46-48]. compared with 34% in Caucasians[49]. Low levels of HDL-C (< 40 mg/dL) were seen in up to a third of South Asians. In a cross-sectional epidemiological descriptive study with 459 Indian subjects in New Delhi, HDL-C levels < 40 mg/dL were seen in 37% of subjects[45].

Enas *et al*[5] compared HDL-C levels in 580 Asian Indian immigrants in the United States with those of native Caucasians in the Framingham Offspring Study. The mean levels of HDL-C were 38 mg/dL in Asian Indian men compared with 46 mg/dL in Caucasian men ($P < 0.001$). Similar results were seen in women, with mean HDL-C levels of 48 mg/dL in Asian Indian women compared with 56 mg/dL in Caucasian women ($P < 0.001$). Ehtisham *et al*[50] compared 64 white European with 65 South Asian healthy adolescents. Mean HDL-C levels were 65 mg/dL in European women compared with 58 mg/dL in South Asian women ($P = 0.001$), whereas they were 54 mg/dL in European men compared with 50 mg/dL in South Asian men ($P = 0.001$). Similarly, in the INTERHEART study, HDL-C levels were the lowest in the South Asian population, at 32.5 mg/dL in cases and

Table 2 Summary of lipoprotein abnormalities in South Asians

CAD occurs with relatively lower levels of LDL-C among South Asians
At any given LDL-C level, South Asians tend to carry a higher total atherogenic burden (*i.e.*, higher levels of apo B and a higher LDL particle concentration)
South Asians tend to suffer from atherogenic dyslipidemia (*i.e.*, high triglyceride and low HDL-C levels) more frequently compared with other ethnic groups
In South Asians, higher HDL-C levels may not be as protective against CAD as in other ethnic groups
In South Asians, HDL particles tend to be smaller and dysfunctional
South Asians have a genetic tendency for elevated atherogenic Lp(a) levels

Apo B: Apolipoprotein B; CAD: Coronary artery disease; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; Lp(a): Lipoprotein(a).

33.5 mg/dL in controls, compared with other Asian and non-Asian groups. More than 80% of both cases and control subjects in South Asia had low HDL-C levels [HDL-C < 40 mg/dL (men) and < 50 mg/dL (women)][22]. These results indicate that the prevalence of low HDL-C levels is much higher in South Asians compared with other ethnic groups.

High triglyceride and low HDL-C levels are metabolically interlinked. This metabolic phenotype is also associated with increased levels of small LDL particles despite relatively normal levels of LDL-C among South Asians. This clinical syndrome is accompanied by insulin resistance, a condition frequently referred to as atherogenic dyslipidemia, which is a common metabolic derangement among Asian Indians[5,31,36,45,50-52]. Rashid *et al*[53] compared lipid levels among South Asians and Europeans (n = 244 and 238, respectively) and all elements of atherogenic dyslipidemia were more severe in South Asians compared to Europeans. Mean triglyceride level was 174 mg/dL *vs* 136 mg/dL (P < 0.0001), LDL-C level was 129 mg/dL *vs* 122 mg/dL (P < 0.02), and HDL-C level was 39 mg/dL *vs* 46 mg/dL among South Asians and Europeans, respectively (P < 0.0001).

These studies indicate that atherogenic dyslipidemia is more prevalent and severe among South Asians and may partially explain the increased CHD risk in this population despite relatively normal levels of LDL-C compared with other ethnic groups.

HDL PARADOX IN SOUTH ASIANS

Higher HDL-C levels have been shown to be associated with a lower risk of CHD[22,27,28,44]. In the INTERHEART study, higher HDL-C levels were associated with a decreased risk of AMI in South Asians. However, the protective effect of higher HDL-C levels seemed to be weaker for South Asians (with OR crossing unity) compared with other Asians in the INTERHEART study (OR for risk of first AMI per 1-SD increase in HDL-C in South Asians: 0.87, 95%CI: 0.72-1.06; OR for rest of Asia: 0.77, 95%CI: 0.70-0.85)[22]. Other investigators have also shown a similar lack of protective effect of HDL-C among South Asians. In a community-based cross-sectional study assessing the correlation of risk factors with carotid intima-media thickness (CIMT) among South Asians from India (n = 303) and Caucasians from Australia (n = 1111), increasing HDL-C levels were associated with decreasing CIMT in the Australian population, but the reverse was true for the Indian population (P < 0.001)[54]. Therefore, South Asians not only have low levels of HDL-C but also appear to have much less cardiovascular protection from HDL-C compared to other ethnic groups.

Why HDL loses its cardioprotective properties in South Asians is unclear. One proposed mechanism is presence of dysfunctional HDL particles. In a small study, Dodani *et al*[55] examined 30 South Asian immigrants and found that 50% had dysfunctional HDL (as determined by using HDL inflammatory index). Presence of dysfunctional HDL correlated with subclinical atherosclerosis measured by CIMT (P = 0.03)[55]. This finding was supported by recently published data from the same authors on 130 South Asian immigrants who underwent HDL function assessment and CIMT measurements; 26% had dysfunctional HDL defined as HDL inflammatory index value of 1 or greater. Presence of dysfunctional HDL correlated with CIMT measurement (P < 0.0024)[56].

It is postulated that metabolic syndrome may render HDL pro-inflammatory[57]. The association between dysfunctional HDL particles and atherosclerosis in South Asians could be potentially explained by a high prevalence of metabolic syndrome in South Asians[19]. However, this might be a noncausal association, and HDL dysfunction indeed may be the result of a diffuse atherosclerotic process[58-62]. What causes HDL to become dysfunctional in South Asians and whether dysfunctional HDL is a true risk factor for increased cardiovascular risk in South Asians is not known. In addition, how much the higher prevalence of metabolic syndrome in South Asians contributes to this effect is not entirely clear. Studies with large sample size are needed to further address this important question.

HDL SUBFRACTIONS IN SOUTH ASIANS

Another potential explanation for the apparent blunted cardioprotection of HDL in South Asians might be related to HDL particle size. Similar to LDL, HDL is composed of heterogeneous particles, with large particles performing highly efficient reverse cholesterol transport, whereas small particles might be less efficient in reverse cholesterol transport. In general, HDL particle size tends to be lower in patients with CHD and those with low HDL-C levels[55].

The role of HDL and other proteins in reverse cholesterol transport is of crucial importance for cholesterol clearance. Cholesterol is removed from vascular endothelial cells and tissue macrophages through a reverse transport process, in which receptors on the HDL surface, such as apo A-I, bind free cholesterol, which is then

carried to the liver and secreted into the bile[63-65]. HDL2b is a major HDL subfraction that is larger in size and may be more efficient in reverse cholesterol transport[30]. Superko *et al*[30] investigated the prevalence of metabolic disorders among Asian Indian and non-Asian Indian males. The standard lipid measurements did not discriminate between groups. However, the levels of HDL2b were significantly lower (12 mg/dL *vs* 14 mg/dL, respectively, $P = 0.0002$) and the prevalence of low HDL2b subfraction (< 20% of total HDL) was higher among Asian Indians compared with non-Asian Indians (92% *vs* 76%, respectively, $P < 0.0002$), suggesting impaired reverse cholesterol transport in South Asians. Bhalodkar *et al*[31] compared various lipoprotein concentrations and sizes between 211 healthy Asian Indian men and 1684 Caucasian men from the Framingham Offspring Study. Asian Indians had significantly lower concentrations of large HDL particles (21 mg/dL *vs* 24 mg/dL, respectively, $P < 0.005$), higher concentrations of small HDL particles (20 mg/dL *vs* 17 mg/dL, respectively, $P < 0.0001$), and smaller HDL particle size (8.5 nm *vs* 8.9 nm, respectively, $P < 0.0001$) compared with Caucasian men.

Therefore, small HDL particle size potentially resulting in inefficient reverse cholesterol transport may be more common in South Asians than in other populations and could partially explain the observed weaker association between HDL-C and cardiovascular events in South Asians compared with other ethnicities. As discussed previously, prospective studies with large sample size are needed to assess further the association between HDL particle size and future risk for cardiovascular disease in South Asians. It is important to note that in the studies described above, HDL particle size was used a surrogate for HDL's reverse cholesterol transport function and no direct measurement of reverse cholesterol transport (*e.g.,* HDL's efflux capacity) was performed.

Lipoprotein(a)

Lipoprotein(a) [Lp(a)] is a highly atherogenic and has been associated with premature atherosclerosis in coronary, cerebral, and peripheral arteries[66-73]. Lp(a) levels are primarily genetically determined, and South Asian immigrants have Lp(a) levels that are similar to those in their counterparts in their home country[71-74] and higher than those in Caucasians. Bhatnagar *et al*[9] compared Lp(a) levels of Indian immigrants in West London with their siblings in Punjab and found that Lp(a) concentrations were similar in both the West London Indian and Punjab populations, but were significantly higher ($P = 0.01$) than those of a white European population in London.

A comparative study of African American, Asian Indian American, and Caucasian American women ($n = 70$ for each) was performed by Palaniappan *et al*[75]. In this study, African Americans had the highest Lp(a) levels, followed by Asian Indian Americans and Caucasian Americans [(Lp(a) 0.5 g/L, 0.3 g/L, and 0.2 g/L, respectively, $P = 0.0001$]. Kamath *et al*[76] also compared Lp(a) levels in 47 South Asian women with those in 47 American women. Lp(a) levels were higher in South Asian women compared with American women [median level (range): 50.7 (2.9-323) nmol/L *vs* 18.3 (2.9-196) nmol/L, respectively, $P < 0.012$]. Anand *et al*[77] performed 3 separate studies comparing Lp(a) levels in South Asians and Caucasians living in North America. The first study included a group of South Asian physicians aged 40-57 years who attended an annual meeting in North America, whose Lp(a) levels were compared with those of their North American counterparts ($n = 141$ and 138, respectively). The mean Lp(a) concentration for South Asian physicians was 19.6 mg/dL compared with 17.5 mg/dL for Caucasian North American physicians ($P = 0.55$). The second study compared 255 South Asian churchgoers aged 22-70 years with 246 Caucasian Americans. The mean Lp(a) concentration was significantly elevated in South Asians (20.2 mg/dL) compared with Caucasian Americans (16.3 mg/dL, $P < 0.002$). In the third study, 30 South Asians and 21 Caucasians who were randomly sampled from the community in Canada were compared. South Asian Canadians had significantly higher mean Lp(a) concentrations compared with Caucasian Canadians (34.1 *vs* 17.3 mg/dL, $P < 0.013$). Therefore, Lp(a) levels in South Asian North Americans are higher than those in Caucasian North Americans but lower than in African Americans.

In an attempt to evaluate the association between Lp(a) levels and CHD risk, Lp(a) levels were compared in 74 Indian patients with CHD and 53 healthy Indian controls. Patients with CHD had almost 5-fold higher Lp(a) levels compared with controls (105 ± 565 mg/dL *vs* 23 ± 76 mg/dL, $P < 0.01$)[78]. In another study, Lp(a) levels were measured in 50 South Asian patients (< 40 years old) with angiographically documented CHD and an equal number of age-matched healthy South Asian controls. In patients with angiographically confirmed CHD, mean Lp(a) levels were significantly higher than in controls (35 mg/dL *vs* 20 mg/dL respectively, $P < 0.002$). Multiple regression analysis showed that elevated Lp(a) level was independently associated with presence of CHD among South Asians (OR = 3.06, 95%CI: 1.24-7.55; $P < 0.001$)[79]. Similarly, Gupta *et al*[80] compared Indian patients with angiographically confirmed CHD with age- and sex-matched Indian controls. Lp(a) concentration was higher in the CHD group ($n = 77$) compared to the control group ($n = 24$) (27 mg/dL *vs* 15 mg/dL, $P < 0.05$). Furthermore, Lp(a) values had a graded association with CHD. The prevalence of CHD in the first (< 5 mg/dL), second (5-25 mg/dL), third (26-75 mg/dL), and highest quartile (≥ 76 mg/dL) of Lp(a) levels was 66.7%, 69.0%, 87.5%, and 100%, respectively[80].

Overall, these studies point towards a genetic tendency for elevated Lp(a) levels in South Asians. These elevated Lp(a) levels correlate with presence of CHD and might partially explain the population-attributable risk for excessive CHD in this group.

TREATMENT OF DYSLIPIDEMIA IN SOUTH ASIANS

Data on the management of dyslipidemia in South Asian subjects are sparse despite the critical importance of dyslipidemia as a cardiovascular risk factor in this population. In the United States, the lipid management guideline developed by the American College of Cardiology/American Heart Association in 2013 is used for management of dyslipidemia[81]. Chandra *et al*[82] recently published a consensus statement regarding dyslipidemia management in Indian subjects. The vast majority of recommendations are extrapolated from the current Western guidelines, because of the paucity of primary data in South Asian populations.

Statin therapy

LDL-C-lowering therapy with statins is the mainstay in the pharmacological treatment of hypercholesterolemia in South Asians, with a suggested LDL-C goal of < 100 mg/dL in high-risk patients and < 70 mg/dL for very-high-risk patients as per a recent consensus statement[82]. There are no South Asian-specific treatment goals or thresholds, given the absence of prospective outcomes data, and thus, these goals were derived from studies mostly performed in Caucasian populations.

In a study in 33 South Asians with hyperlipidemia, a target LDL-C goal of < 77 mg/dL was achieved in 81% of patients after 4 wk treatment with 10 mg/d atorvastatin, without statin-related adverse effects being noted[83]. Similarly, a study in patients with established CHD on statins compared the efficacy and safety of atorvastatin and simvastatin in South Asians and Caucasians. Atorvastatin (median dose = 20 mg/d in both groups) produced similar decreases in LDL-C in South Asian (43%) and Caucasian (41%) patients and increased in HDL-C by 19% in South Asians and by 12% in Caucasians (P = NS). Simvastatin (median dose = 20 mg/d in both groups) reduced LDL-C by 35% in South Asians and by 37% in Caucasians while raising HDL-C by 12% in both groups (P = NS). Both medications were well tolerated[84].

The Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration study was a 12 wk prospective, open-label study in patients at high risk for atherosclerosis (European origin: n = 1978; South Asian origin: n = 64). After propensity matching, atorvastatin lowered LDL-C to a similar degree in both groups (reduction in LDL-C from baseline was 34% in South Asians compared with 38% in Europeans, P = 0.22), with no differences in safety observed[85]. Furthermore, postmarketing data for statins have not identified any particular safety issues with statins in South Asians[86].

Other studies performed head-to-head comparisons among different statins in South Asians. Jayaram *et al*[87] compared the use of rosuvastatin 10 mg/d with atorvastatin 10 mg/d in adult Indian patients with dyslipidemia (mean LDL-C > 160 mg/dL and triglyceride > 400 mg/dL). The fall in the mean LDL-C levels after 6 wk of treatment in the rosuvastatin group was 40%, compared with 30% in the atorvastatin group. This higher efficacy of rosuvastatin in terms of LDL-C lowering was further tested in the Investigation of Rosuvastatin in South Asians study. In this randomized trial, 740 patients of South Asian origin living in United States and Canada received 6 wk of treatment with either rosuvastatin (10 or 20 mg/d) or atorvastatin (10 or 20 mg/d). A total of 485 patients (66%) were categorized as being at high risk for CHD, with a National Cholesterol Education Program Adult Treatment Panel Ⅲ treatment goal of LDL-C < 100 mg/dL. LDL-C levels decreased by 45% with rosuvastatin 10 mg *vs* 40% with atorvastatin 10 mg (P = 0.002) and by 50% with rosuvastatin 20 mg *vs* 47% with atorvastatin 20 mg (P = NS). National Cholesterol Education Program Adult Treatment Panel Ⅲ LDL-C goal attainment rates in high-risk patients were 76% (79%) and 88% (89%) with rosuvastatin 10 (20 mg), respectively, compared with 70% (76%) and 81% (85%) with atorvastatin 10 (20 mg), respectively. Rosuvastatin and atorvastatin were both well tolerated[88].

In a pharmacokinetic study of rosuvastatin, both lasting time in serum and peak plasma concentrations were higher in Asian Indians compared with non-Asian-Indians living in Singapore (P < 0.0001)[89]. This lower statin metabolism has raised a concern about increased side effects of statins in South Asians, especially with higher doses. The United States Food and Drug Association-approved highest doses of statin are, therefore, lower for Asians compared with other groups[90], and it might be prudent to start a lower dose of a statin in Asian patients.

Overall, these results point to similar efficacy with statin therapy in South Asians compared with Caucasians, although, based on pharmacokinetic data, the maximum approved dose for rosuvastatin is lower for Asians (including South Asians) compared with other ethnicities. The recommended initiation dose for rosuvastatin is 5 mg once daily, with maximum recommended dose of 20 mg daily, for Asians.

Combination drug therapy

Given the plethora of lipoprotein abnormalities in South Asians, targeting non-LDL lipid fractions may be relevant. Sharma *et al*[91] studied combination therapy of lovastatin and niacin in a prospective multicenter study that included 131 Asian Indians with LDL-C levels ≥ 130 mg/dL. A significant trend was observed in LDL-C lowering (levels at baseline and weeks 4, 12, and 24, respectively: 153, 127, 109 and 95 mg/dL; P < 0.05). The percentage decrease in LDL-C from baseline was 38% at 24 wk. Similarly, HDL-C was increased by 18%, triglycerides were decreased by 21%, and Lp(a) was decreased by 44.5% (P < 0.05) at 24 wk compared with baseline. No significant changes were observed in systolic or diastolic blood pressure, blood creatinine, transaminases, or creatinine kinase, suggesting an acceptable safety profile.

Ezetimibe is a nonstatin medication that lowers plasma levels of LDL-C by inhibiting the activity of the

Niemann- Pick C1-like 1 (NPC1L1) protein. Stitziel *et al*[92] sequenced the exons of NPC1L1 in 7364 patients (844 South Asians) with CHD and in 14728 controls (1107 South Asians). Naturally occurring mutations that disrupt NPC1L1 function were found to be associated with reduced plasma LDL-C levels and a reduced risk for CHD in individuals with various ethnic backgrounds, including South Asians. This finding suggested that inhibitory drugs such as ezetimibe could reduce LDL-C level and CHD risk reduction in South Asians similar to in other populations. In another study, ezetimibe and statin combination therapy was examined in 64 South Asian Canadians with CHD or diabetes and persistent hypercholesterolemia on statin therapy. Patients were randomized to receive ezetimibe 10 mg/d coadministered with statin therapy or a doubling of their current statin dose. At 6 wk, the proportion of patients achieving target LDL-C (< 77 mg/dL) was significantly higher among the ezetimibe + statin-treated patients compared with the statin-doubling group (68% *vs* 36%, respectively; P = 0.031) with an OR (95%CI) of 3.97 (1.19-13.18), accounting for baseline LDL-C levels and adjusting for age. At 12 wk, 76% of ezetimibe + statin patients achieved target LDL-C compared with 48% of the patients in whom statin dose was doubled (adjusted OR = 3.31, 95%CI: 1.01-10.89; P = 0.047). No serious adverse effects were recorded[93]. Despite these findings, it is important to note that the current cholesterol treatment guidelines recommend the use of maximum tolerated statin dose before adding a second LDL-C-lowering agent.

Combination therapy targeting various dyslipidemias in South Asians appears to be promising. Prospective studies with large sample size and longer follow-up period are needed to assess accurately the efficacy and safety profile of these agents in South Asian populations. Importantly, data are needed to assess whether the use of combination therapy improves cardiovascular outcomes in this patient population with a specific need for combination therapy, given the high prevalence of atherogenic dyslipidemia as discussed above.

CONCLUSION

South Asians have a high CHD prevalence and suffer from early-onset CHD compared with other ethnic groups. Conventional risk factors may not fully explain the increased CHD risk in this population. Indeed, South Asians have a unique lipid profile which may predispose them to premature CHD. The dyslipidemia in South Asians is most importantly characterized by elevated levels of triglycerides, low levels of HDL-C, elevated Lp(a) levels, and a higher atherogenic particle burden despite relatively normal LDL-C levels. HDL particles appear to be smaller, dysfunctional, and proatherogenic in South Asians. Despite the rapid expansion of the current literature with better understanding of the specific lipid abnormalities in this patient population, studies with adequate sample sizes are needed to assess the significance and contribution of a given lipid parameter on overall cardiovascular outcomes in this patient population. Specific lipid management goals and treatment thresholds do not exist for South Asians due to the paucity of data. Current treatment recommendations are mostly extrapolated from Western guidelines. Lastly, large, prospective studies with outcomes data are needed to assess cardiovascular benefit associated with various combination therapies in this patient population.

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REVIEW

Exercise oscillatory ventilation: Mechanisms and prognostic significance

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Abstract

Alteration in breathing patterns characterized by cyclic variation of ventilation during rest and during exercise has been recognized in patients with advanced heart failure (HF) for nearly two centuries. Periodic breathing (PB) during exercise is known as exercise oscillatory ventilation (EOV) and is characterized by the periods of hyperpnea and hypopnea without interposed apnea. EOV is a non-invasive parameter detected during submaximal cardiopulmonary exercise testing. Presence of EOV during exercise in HF patients indicates significant impairment in resting and exercise hemodynamic parameters. EOV is also an independent risk factor for poor prognosis in HF patients both with reduced and preserved ejection fraction irrespective of other gas exchange variables. Circulatory delay, increased chemosensitivity, pulmonary congestion and increased ergoreflex signaling have been proposed as the mechanisms underlying the generation of EOV in HF patients. There is no proven treatment of EOV but its reversal has been noted with phosphodiesterase inhibitors, exercise training and acetazolamide in relatively small studies. In this review, we discuss the mechanistic basis of PB during exercise and the clinical implications of recognizing PB patterns in patients with HF.

Key words: Exercise; Oscillatory ventilation; Heart failure

Core tip: Alteration in breathing patterns in patients with advanced heart failure (HF) characterized by cyclic variation of ventilation with a period of approximately one minute is known as periodic breathing. Periodic breathing during exercise, known as exercise oscillatory ventilation (EOV), is an oscillatory ventilatory pattern during

exercise that persists for at least 60% of the exercise test with an amplitude ≥ 15% of the average resting value. Circulatory delay, pulmonary congestion and chemoreceptor sensitivity has been proposed to cause generation of EOV. EOV is found to be an independent predictor of worse outcome irrespective of other gas exchange variables in HF patients.

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INTRODUCTION

Impaired cardiac filling or ejection of the blood are the cardinal features of heart failure (HF) which leads to multiple organ systems dysfunctions[1] with dyspnea on exertion and exercise intolerance being the most common. Alteration in breathing patterns with cyclic variation of breathing secondary to instability in respiratory control has been a recognized feature of HF for almost two centuries[2,3]. Cheyne[2] (1818) first described a severe form of disordered breathing during rest characterized by alternating hyperpnea and hypopnea with intervals of apnea lasting almost a minute in a patient with HF and similar case was described by Stokes[3] nearly three decades later (1854) after which the condition was named Cheyne-Stokes breathing.

Periodic breathing (PB) characterized by cyclic variation of ventilation with or without interposed apnea have been observed at rest[4], during sleep[4-7] and during exercise[8-10] (Figure 1) in HF patients. Sleep disordered breathing such as obstructive sleep apnea (OSA) and central sleep apnea (CSA) has been observed in nearly 50% of stable HF patients[6] with CSA being significantly more prevalent (40%) than OSA. In one study, the presence of sleep disordered breathing at night was accurately predicted by concomitant daytime PB (AUC 0.821, $P < 0.01$ at receiver operating characteristic analysis, sensitivity 75%, specificity 75%)[4].

An unusual crescendo-decrescendo ventilatory response to exercise in patients with heart disease without resting Cheyne-Stokes breathing was initially reported by Weber[11] and further described by Kremser *et al*[12] in 1987. This phenomenon of periodic oscillatory breathing during exertion without interposed apnea is now known as exercise PB or exercise oscillatory ventilation (EOV) (Figure 2). EOV has recently been recognized in significant percentage of symptomatic HF patients, both with reduced[4,9,10,12-17] and preserved[18] left ventricular ejection fraction (LVEF). Despite the frequent occurrence of PB in patients with HF, pathophysiologic mechanisms that induce irregular breathing as well as the therapeutic modalities to reverse this condition in HF still remain incompletely understood. In this review, we focus specifically on EOV discerned in the context of measuring expired gas exchange variables during exercise through cardiopulmonary exercise testing.

CARDIOPULMONARY EXERCISE TESTING AND EOV

Cardiopulmonary exercise testing (CPET) provides a unique opportunity to evaluate patient's aerobic capacity with breath-by-breath expired gas parameters[19]. Besides providing information about patient's functional capacity with peak oxygen uptake (VO_2)[20], CPET is also helpful in delineating pulmonary vascular abnormalities in HF patients. Studies have shown that ventilatory efficiency (V_E/VCO_2 slope)[21,22] is even better predictor of HF outcomes than peak VO_2. EOV on the other hand is discerned in HF patients during submaximal exercise which makes it a very attractive CPET parameter in those patients who are not able to complete maximal effort exercise testing.

EOV

Definitions

Presence of EOV during CPET is identified by ventilatory oscillations with a typical cycle length and amplitude but there are a lot of variations on its definition[23]. Cycle length of an oscillation in V_E is the time between nadirs of two ventilatory oscillations and the amplitude of oscillation is the difference between the peak V_E during an oscillation and the nadirs in V_E (Figure 2)[24]. Some of the definitions used for EOV are: (1) Kremser *et al*[12] and Corrà *et al*[10,13]: Oscillations in V_E with a cycle length of approximately 1 min, amplitude > 15% of resting V_E, and duration > 60% (> 66%[12]) of exercise duration; (2) Ben-Dov *et al*[25]: 3 or more consecutive regular oscillations in V_E with oscillation amplitude > 25% of average V_E and cycle length 30-60 s; (3) Leite *et al*[15]: Three or more cycles of regular oscillation in V_E with standard deviation of 3 consecutive cycle lengths within 20% of the average and minimal average amplitude of oscillation > 5 L/min; and (4) Sun *et al*[24]: Three or more consecutive cyclic fluctuations in V_E, amplitude > 30% of concurrent mean V_E, oscillation of ≥ 3 gas exchange variables, cycle length of 40-140 s.

The American Heart Association consensus statement has defined EOV as an oscillatory ventilatory pattern that persists for at least 60% of the exercise test at amplitude 15% or more of the average resting value[19]. Due to the lack of automated measurement methods, presence of EOV during CPET is usually analyzed manually which may have lead to variations in its definitions and appropriate identification. More recently custom software has been used to identify EOV during exercise[26,27].

Prevalence of EOV

The prevalence of EOV has been different based on

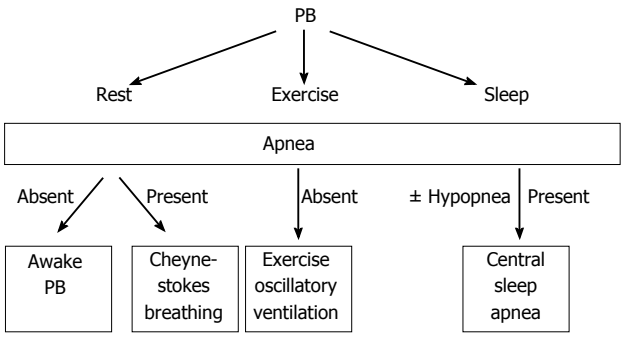

Figure 1 Types of periodic breathing in heart failure patients. PB: Periodic breathing.

the severity and type of HF patient population studied. Patients with HF with reduced ejection fraction (HFrEF) has been found to have EOV prevalence of 12%-58% [8-10,12,13,15,16,18,24,28]. We found EOV prevalence of 45% in a subset of patients with HFrEF (n = 56, mean ± SD: LVEF = 30% ± 6%, peak VO_2 = 12.4 ± 0.5 mL/kg per minute)[8]. EOV is similarly common in patients with HF and preserved ejection fraction (HFpEF)[18,29-31] with one previous study reported prevalence of 31%[18]. Olson *et al*[29] found that 41% of HF patients with EOV had LVEF ≥ 40%, and in the study by Matsuki *et al*[30] the mean LVEF in HF patients with EOV was 41.3 ± 16.3.

Mechanisms of generation of EOV

There is limited data regarding the mechanistic basis for EOV despite its significant association with poor outcomes in HF patients[32]. The control of the normal ventilation is through the feedback loop between pulmonary gas exchanging capillaries and peripheral chemoreceptors located in the carotid bodies and the central chemoreceptors located in the medulla (Figure 3)[33-37]. Any instability of this ventilatory regulation can lead to generation of oscillatory respiratory pattern. The generation of crescendo and decrescendo respiratory pattern can be caused by: (1) Circulatory delay (*i.e.,* increased circulation time from the lung to the brain and chemoreceptors due to reduced cardiac index leading to delay in information transfer)[15,36,37]; (2) increase in controller gain (*i.e.,* increased central and peripheral chemoreceptor sensitivity to $PaCO_2$ and PaO_2)[14,35,38]; or (3) reduction in system damping (*i.e.,* baroreflex impairment) (Figure 3). The possible mechanisms responsible for generation of PB during exercise (*i.e.,* EOV) have largely been extrapolated from studies of PB at rest[39] and during sleep[15,40] even though there has been limited overlap between PB during exercise and during sleep[13].

Circulatory delay: Reduced cardiac output in patients with HF increases the circulation time from lungs to chemoreceptors and respiratory centers. This delayed transfer of information has been postulated to generate late feedback signals leading to oscillations in ventilation[41]. Hypotension and circulatory delay has been shown to induce cardiorespiratory oscillations in experimental rat models[42]. Similarly reduced resting CI and prolonged lung-to ear circulation time (LECT) were the major determinants of PB at rest in HF patients in one previous study[43]. LVEF has also been noted to be significantly lower in HF with PB compared to those without PB[44]. Delayed generation of respiratory and pulmonary blood flow oscillations during exercise compared to LVEF fluctuations in HF patients also supports delayed circulation causing alterations in respiratory feedback mechanisms[45].

In a study of 56 HFrEF patients, those with EOV demonstrated a greater degree of hemodynamic impairment both at rest and during exercise and had 25% lower cumulative CI compared to HF patients without EOV[8]. The amplitude and duration of oscillations were inversely related to exercise CI, and the changes in cycle length and amplitude of EOV after 12 wk of treatment with sildenafil were inversely related to changes in CI[8]. In another small study (n = 17, age 68 ± 12 years), patients with advanced HF, as reflected by a lower peak VO_2 and higher V_E/VCO_2 slope, had a longer cycle length of ventilatory oscillations and a longer phase difference between oscillating VO_2 and V_E[46]. Attenuation of EOV during high-intensity exercise could be due to increased CI during exercise leading to reduced circulation time which supports circulatory delay as an important determining factor for the generation of EOV. However, some investigators have argued against contribution of circulatory delay to EOV but did not directly measure cardiac output or circulation time[45].

Increased chemosensitivity: Increased carotid and aortic chemoreceptor sensitivity to minimal changes in arterial O_2 and CO_2 may contribute to sympathetic overactivity which leads to excessive and irregular ventilation during exercise[47]. Enhanced hypoxic and central hypercapneic chemosensitivity may cause increased ventilatory response (V_E/VCO_2) to exercise in HF patients[48]. Such chronically increased ventilation causes reduction in arterial concentration of both CO_2 and bicarbonate[49] which weakens the blood's ability to buffer against changes in CO_2 levels leading to overly sensitive ventilatory control system. Pitt *et al*[50] in 1907 observed that a modest increase in partial pressure of CO_2 triggers a cycle of hyperventilation-induced reduction in $PaCO_2$ until the apnea threshold is reached leading to Cheyne-Stokes breathing. In a quantitative algebraic analysis of the dynamic cardiorespiratory physiology, circulatory delay and increased chemoreflex gain were found to be the primary factors causing EOV[47]. In both experimental cat models and stable HF patients, inhalation of 100% O_2 decreased the peripheral chemoreceptor discharge and thus oscillatory ventilation[34,42]. Steens *et al*[51] noticed that inhalation of 3% CO_2 virtually eradicated Cheyne Stokes Respiration in HFrEF patients with stable NYHA class Ⅲ-Ⅳ symptoms. Similarly dihydrocodeine attenuated PB by reducing chemosensitivity in 42% of HF patients[34].

Despite the proposed mechanism of increased peripheral chemoreceptor sensitivity causing EOV, there may be other non-peripheral chemoreceptor mediated

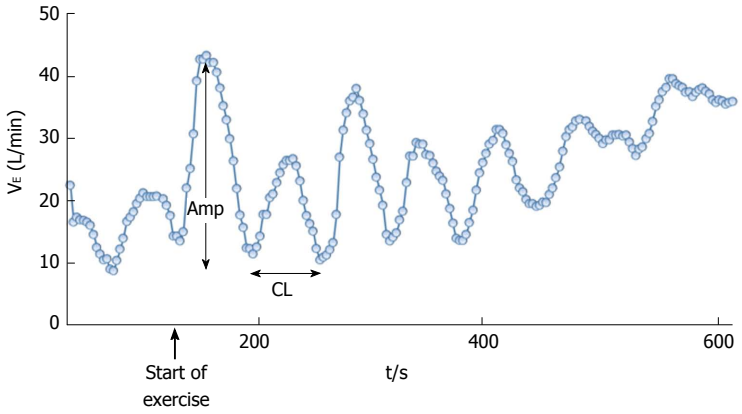

Figure 2 Oscillatory ventilation during exercise. CL: Cycle length; Amp: Amplitude of oscillation; V_E: Ventilation.

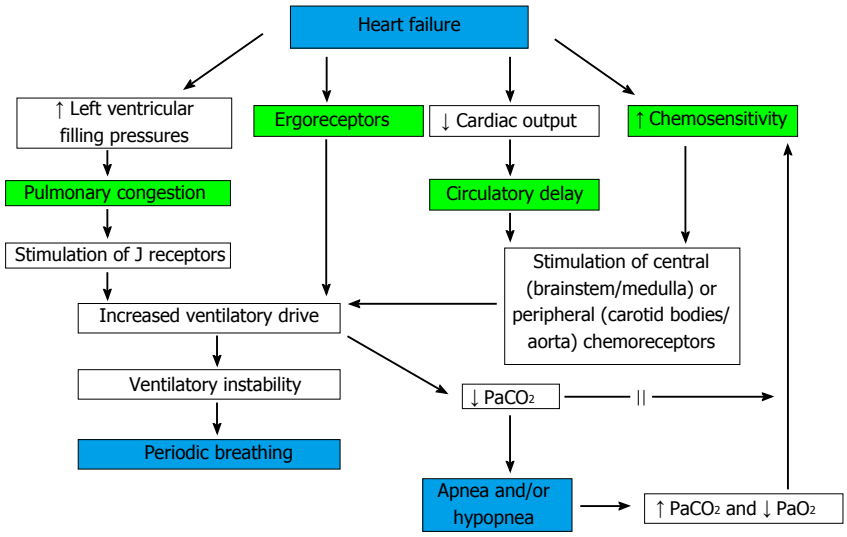

Figure 3 Mechanisms of generation of periodic breathing in heart failure patients.

mechanisms involved in mediating increased ventilatory response to exercise[52]. In one study of HFrEF patients, arterial blood gases ($PaCO_2$ and PaO_2) at rest and average values across the first 6 min of exercise in HF patients had no relationship with EOV[8]. The amplitude and duration of EOV was also not related to mean $PaCO_2$ which argues against a $PaCO_2$ set point close to the apnea threshold, serving as a major determinant of the presence of EOV in HF patients[8].

Pulmonary congestion: Pulmonary congestion[53] and decreased lung compliance[54] has been postulated to cause overstimulation of the ventilatory control center which leads to hyperventilation and decrease in PCO_2[55] and thus generating PB. Elevated pulmonary capillary wedge pressure, a surrogate marker for pulmonary congestion, stretches pulmonary C fibers (J receptors)[56] which in turn stimulates the medullary respiratory center *via* vagal afferents[57], leading to rapid shallow breathing, hypocapnia, and initiation of PB at rest. The damping effects of O_2 and CO_2 stores which prevent oscillations are also reduced by pulmonary congestion and a small fluctuation in CO_2 level makes the respiratory control unstable in HF patients with pulmonary congestion[37]. In 1943, Christie *et al*[58] were able to induce PB due to pulmonary congestion by occluding a pulmonary vein. Recent findings of increased resting and exercise cardiac filling pressures[8,30] and higher NT-proBNP[30] levels in HF patients with EOV compared to those without EOV extends their findings. Despite these findings suggestive of role of pulmonary congestion as the etiology for EOV, this mechanism has been questioned by some investigators[45] which noticed disappearance of EOV during later exercise in HF patients despite an increase in PCWP.

Ergoreflex signaling: HF causes metabolic and structural abnormalities in the skeletal muscles which may also lead to enhanced ergoreflex signaling during exercise which has been postulated as an etiologic factor for generation of PB. Increased ergoreflex may be associated with worse NYHA class, decreased exercise tolerance, and hyperventilation during exercise in HF patients[59-61]. In a study by Pardaens *et al*[62], ergoreflex

activity contributed to hyperventilation in HF patients with a history of recent decompensation or persistent symptoms. Oscillations in output of neurologic stimuli from the medullary vasomotor center may explain disappearance of respiratory oscillations found at rest or at low levels of exercise during more intense exercise[43]. Decreased activation of both CO_2 chemoreflex and the ergoreflex has recently been shown to decrease ventilatory drive after cardiac resynchronization therapy[63]. Despite the proposed contribution of ergoreceptors to the autonomic, hemodynamic, and respiratory responses to exercise in HF patients, further investigation is needed to establish its relationship to hyperventilation and EOV in HF patients.

Prognostic Significance of EOV

It has been well known that the prevalence of EOV tracks with the metrics of HF severity such as higher NYHA class, lower peak VO_2, higher V_E/VCO_2 slopes and lower $PETCO_2$[8,12,13,15,16,24,28-30,64-69] (Table 1). EOV actually provides strong independent prognostic information regarding the severity of HF even after adjustment for these variables. The initial study describing the prognostic significance of PB by Ponikowski *et al*[34] predicted poor 2-year survival in HF patients with abnormal breathing patterns which was independent of peak VO_2 and NYHA class. Similarly Bard *et al*[17] also observed resting ventilatory variation to be the best predictor of mortality in 44 matched HFrEF patients. Leite *et al*[15] and Corrà *et al*[10,13] both found that HF patients with EOV had 3-fold higher mortality compared to those without EOV (Table 1). When EOV is present along with other abnormal ventilatory patterns either during sleep or during exercise, the risk of mortality increases even further as those observed by Corrà *et al*[13] in a group of HF patients who had abnormal breathing patterns during sleep and EOV during exercise (54% adverse events in patients with EOV and apnea hypopnea index > 30/h *vs* 17% with EOV alone, OR = 6.65, 95%CI: 2.6-17.1, $P < 0.01$). Similarly the odds of dying in 6 mo increased by 4-fold (9.4 to 38.9) when EOV was present along with elevated V_E/VCO_2 slope in another group of HF patients[24]. EOV is not only known to be the independent predictor of overall mortality and sudden cardiac death in HFrEF patients but also the strongest predictor of mortality in HFpEF patients in multivariate models[9]. Ingle *et al*[28] observed EOV to be the predictor of mortality independent of peak VO_2, V_E/VCO_2 slope, LVEF, age, and 6-min walking distance. EOV has recently been recognized as a potent prognostic indicator in patients with congenital heart disease as EOV along with the percentage of maximum predicted HR were independent predictors of the combined outcome of death, transplantation or cardiovascular hospitalization in patients who underwent Fontan procedure[27].

The superior prognostic value of EOV and V_E/VCO_2 slope compared to peak VO_2 has been observed in multiple studies examining the relative predictive values of various CPET variables (Table 1). EOV along with other CPET derived variables (V_E/VCO_2 slope, oxygen uptake efficiency slope and ventilatory equivalent for CO_2 nadir) has been shown to outperform the traditional Heart Failure Survival Score in predicting outcomes in patients with mild-to-moderate HF[70]. Guazzi *et al*[71] recently characterized EOV in patients with broader cardiovascular risk factors and found the EOV to be an indicator of worse CV risk factor profile in patients even without clinical manifestations of HF. The feasibility of EOV measurements during submaximal exercise during CPET makes it particularly attractive in HF population who are unable to do maximum effort exercise testing.

EOV reversibility

Various pharmacological or surgical interventions has been performed in HF patients to identify the potential reversibility of EOV but there has not been any large scale clinical trial with EOV as the primary endpoint. In a small randomized double-blind placebo controlled trial of HFrEF patients, serial assessment of EOV before and after 12 wk of sildenafil treatment showed reduction in EOV cycle length and oscillatory amplitude and increase in exercise CI in the sildenafil group compared to placebo[8]. The changes in oscillatory cycle length and amplitude after sildenafil treatment were inversely related to changes in exercise CI[8]. This finding was further supported by another study from Guazzi *et al*[18] who noted resolution of EOV in the majority of patients treated with sildenafil, although EOV was not a pre-specified endpoint in these trials with small number of study subjects ($n < 40$).

Attenuation of PB has been observed with valvular[72] and open heart surgeries, and cardiac transplantation[73]. There are few other studies involving small number of patients that showed resolution of EOV with different therapeutic interventions. For example, Ribeiro *et al*[74] noticed reduction in EOV with phosphodiesterase-3 inhibitor milrinone in three patients and Castro *et al*[75] reported reversal of EOV and improvement in NYHA class with exercise training in one HF patient despite no change in LVEF. Reversal of EOV in 71% of stable HFrEF patients has also been observed after 3 mo of outpatient exercise training program[76]. This highlights the importance of exercise therapy in both HFrEF and HFpEF patients. Recent studies have shown that inhalation of CO_2[77] and acetazolamide[77,78] treatment significantly reduced PB during exercise in HF patients. Kazimierczak *et al*[67] noticed reversal of EOV in more than 85% of the HF patients after three months of nocturnal adaptive servoventilation even though it was a very small study ($n = 8$). Finally, in an experimental study of pacing induced-CHF rabbit models, carotid body chemoreceptor denervation reduced disordered breathing patterns[79].

CLINICAL IMPLICATIONS

EOV is a significant prognostic indicator of adverse outcomes in HF patients. EOV identification at submaximal levels of exercise during CPET and the possibility of EOV reversal with HF interventions makes it a potential

Table 1 Prevalence and clinical significance of exercise oscillatory ventilation in heart failure patients

Ref.	No. of patients	NYHA class, LVEF	Prevalence of PB	Clinical and prognostic significance of EOV	Significant mortality predictors
Corrà *et al*[10], (2002)	323	NYHA 2.2 ± 0.9 LVEF 24 ± 8	12%	EOV present in 28% of nonsurvivors *vs* 9% survivors, follow-up period 22 ± 11 mo	NYHA class, LVEF, peak VO_2
Leite *et al*[15], (2003)	84	NYHA 2-4 LVEF 35 ± 7	30%	EOV independently increased the risk of death by 2.97 fold, median follow-up period of 11.3 mo	Peak VO_2, NYHA class, V_E/VCO_2 slope
Corrà *et al*[13], (2006)	133	NYHA 2.3 ± 0.7 LVEF 23 ± 7	21%	42% mortality in EOV patients *vs* 15% in non EOV, follow-up period 39 ± 11 mo	NYHA class, peak VO_2, V_E/VCO_2 slope, AHI, LVEF, lower rate of beta blocker use, peak HR
Guazzi *et al*[9], (2007)	156	NYHA 1-4 LVEF 35 ± 11	33%	EOV was the strongest predictor of overall and SCD mortality. EOV present in 100% arrhythmic and 47% nonarrhythmic deaths, follow-up period 28 ± 25 mo	LV mass, LVESV. V_E/VCO_2 slope maintained a predictive value as to overall cardiac mortality and pump failure death outperforming EOV as predictor of pump failure mortality
Guazzi *et al*[18], (2008)	556 (405 HFrEF, 151 HFpEF)	NYHA 2.4 ± 0.8 in HFrEF, 2.0 ± 0.9 in HFpEF	35% in HFrEF, 31% in HFpEF	EOV was strongest predictor of mortality in HFpEF compared to HFrEF in multivariate models; EOV was similar predictor of mortality in both HFrEF and HFpEF without LVAD or transplant	V_E/VCO_2 slope in multivariate model, peak VO_2 in univariate model
Arena *et al*[16], (2008)	154	NYHA 2.2 LVEF 30 ± 14	36%	Event (death, transplant or LVAD) free survival 55% in EOV *vs* 82% in non EOV patients, follow-up period 3 yr	V_E/VCO_2 slope, LVEF
Bard *et al*[17], (2008)	44	LVEF 19 ± 7	13%	Death or transplant rate 68% in patients with PB *vs* 52% without PB	Resting ventilatory variation more powerful predictor of mortality than peak VO_2 and V_E/VCO_2 slope
Olson *et al*[29], (2008)	47	NYHA 2.6 ± 0.8 LVEF 37 ± 17	7%	EOV associated with higher V_E/VCO_2 slope, V_D/V_T, lower $PETCO_2$, higher NYHA class	
Ingle *et al*[28], (2009)	240	LVEF 34 ± 6	31% by Leite and 25% by Corrá Criteria	50% of patients diagnosed with EOV by Corrá criteria and 58% diagnosed by Leite criteria died within 1 yr	
Sun *et al*[24], (2010)	580	NYHA 2-4 LVEF 26 ± 7	51%	EOV combined with elevated V_E/VCO_2 (≥ 155% predicted) resulted in an OR of 39 for 6 mo mortality	Peak VO_2, AT, peak oxygen pulse significantly worse in nonsurvivors
Ueshima *et al*[68], (2010)	50	NYHA 1-3	28%	EOV associated with lower peak VO_2 and higher V_D/V_T	
Murphy *et al*[8], (2011)	56	NYHA 2-4 LVEF 30 ± 6	45%	EOV related to ↓exercise cardiac output and ↑cardiac filling pressures	
Scardovi *et al*[31], (2012)	370	NYHA 1-3 LVEF 41% (range 34%-50%)	58%	EOV, V_E/VCO_2 slope and its ratio to peak VO_2 predicted all-cause mortality independent of LVEF	Hemoglobin level, creatinine, BMI, HF admissions in the previous year
Matsuki *et al*[30], 2013	46	NYHA 3 LVEF 41 ± 16	44%	EOV patients had ↑cardiac filling pressures, higher NT-proBNP value, ↑V_E/VCO_2 slope, low $PETCO_2$ and greater Borg dyspnea score	
Nathan *et al*[27], (2015)	253	NYHA 1-3	38%	5 yr rate of death or transplant 14.1% in Fontan patients with EOV *vs* 4.1% of those without EOV	NYHA class, peak HR

LVEF and follow-up periods are in mean ± SD. NYHA: New York Heart Association; VO_2: Oxygen uptake; V_E: Ventilator efficiency; AHI: Apnea-hyponea index; AT: Anaerobic threshold; HR: Heart rate; LVEF: Left ventricular ejection fraction; HFrEF: HF and reduced ejection fraction; HFpEF: HF and preserved ejection fraction; HF: Heart failure; OR: Odds ratio; SCD: Sudden cardiac death; LVAD: Left ventricular assist device; LVESV: Left ventricular end systolic volume; $PETCO_2$: End tidal partial pressure of carbon dioxide; V_D/V_T: Ratio of physiologic dead space over tidal volume; BMI: Body mass index; NT-proBNP: N terminal pro brain natriuretic peptide.

surrogate end point of interest for HF clinical trials focused on improvement in gas exchange variables and exercise hemodynamics. There is still a need for HF studies with specific EOV endpoint to identify whether HF interventions such as diuretic therapy, exercise training, phosphodiesterase inhibitors, cardiac resynchronization therapy, intensification of neurohormonal blockade, cardiac surgery or other emerging therapies such as neprilysin inhibitors will successfully attenuate EOV, and if that modification translates into improvement in underlying cardiac dysfunction and clinical outcome of HF patients.

CONCLUSION

EOV is a noninvasive and reproducible exercise parameter which is easily recognizable during submaximal cardiopulmonary exercise testing. EOV has been proven to be a strong predictor of reduced survival in HF patients irrespective of the echocardiographic and gas exchange

variables. Presence of EOV in a HF patient indicates significant impairment in resting and exercise cardiac hemodynamic parameters, especially when the cycle length of EOV is longer than one minute and when EOV occurs early during exercise. HF patients presenting with EOV may therefore need an intensification of therapy to optimize cardiac hemodynamics, and improve overall symptoms and functional capacity.

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REVIEW

Prediction of atrial fibrillation development and progression: Current perspectives

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. Several conventional and novel predictors of AF development and progression (from paroxysmal to persistent and permanent types) have been reported. The most important predictor of AF progression is possibly the arrhythmia itself. The electrical, mechanical and structural remodeling determines the perpetuation of AF and the progression from paroxysmal to persistent and permanent forms. Common clinical scores such as the hypertension, age ≥ 75 years, transient ischemic attack or stroke, chronic obstructive pulmonary disease, and heart failure and the congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65-74 years, sex category scores as well as biomarkers related to inflammation may also add important information on this topic. There is now increasing evidence that even in patients with so-called lone or idiopathic AF, the arrhythmia is the manifestation of a structural atrial disease which has recently been defined and described as fibrotic atrial cardiomyopathy. Fibrosis results from a broad range of factors related to AF inducing pathologies such as cell stretch, neurohumoral activation, and oxidative stress. The extent of fibrosis as detected either by late gadolinium enhancement-magnetic resonance imaging or electroanatomic voltage mapping may guide the therapeutic approach based on the arrhythmia substrate. The knowledge of these risk factors may not only delay arrhythmia progression, but also reduce the arrhythmia burden in patients with first detected AF. The present review highlights on the conventional and novel risk

factors of development and progression of AF.

Key words: Atrial fibrillation; Development; Progression; Risk factors; Inflammation; Fibrosis

Core tip: Atrial fibrillation (AF) is a progressive disease associated with increased morbidity and mortality. Prevention of arrhythmia progression is therefore of paramount importance. An intense rhythm control strategy will prevent structural and electrical remodelling. The modification of common risk factors of AF development and progression such as hypertension, obesity, and sleep apnoea should be additionally considered. Emerging risk factors such as inflammation and fibrosis will guide the therapeutic approach in the future.

Vlachos K, Letsas KP, Korantzopoulos P, Liu T, Georgopoulos S, Bakalakos A, Karamichalakis N, Xydonas S, Efremidis M, Sideris A. Prediction of atrial fibrillation development and progression: Current perspectives. *World J Cardiol* 2016; 8(3): 267-276 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i3/267.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i3.267

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia managed in clinical practice and its incidence increases sharply with age[1]. AF is associated with increased morbidity and mortality that primarily occur as a result of 2 complications: Stroke and heart failure (HF)[2]. Mortality is increased because of a combination of altered hemodynamics, atrioventricular dyssynchrony, progressive atrial and ventricular mechanical dysfunction, and thromboembolic complications. The current evidence indicates that the overall prevalence of AF is in the range of 1%-2% of the general population[3]. Its prevalence is expected to double in the next 50 years as a consequence of prolongation of life[4]. Significant interest has been directed to risk factors predicting the progression of paroxysmal to permanent AF. The knowledge of these risk factors may not only delay AF progression, but also reduce the arrhythmia burden in patients with first detected AF. The present review highlights on conventional and novel risk factors of development and progression of AF.

DEFINITION OF AF

The American College of Cardiology, the American Heart Association, the Asia Pacific Heart Rhythm Society, the European Cardiac Arrhythmia Society, the European Heart Rhythm Association, the Society of Thoracic Surgeons, and the Heart Rhythm Society classified AF as paroxysmal, persistent, longstanding persistent and permanent AF[5]. Paroxysmal AF is defined as recurrent AF (2 episodes) that terminates spontaneously within 7 d. Episodes of AF of 48 h duration that are terminated with electrical or pharmacologic cardioversion should also be classified as paroxysmal AF episodes. Persistent AF is defined as continuous AF that is sustained beyond 7 d. Episodes of AF in which a decision is made to electrically or pharmacologically cardiovert the patient after 48 h of AF, but prior to 7 d, should also be classified as persistent AF episodes. Longstanding persistent AF is defined as continuous AF of greater than 12 mo duration. The term permanent AF is not appropriate in the context of patients undergoing catheter or surgical ablation of AF, as it refers to a group of patients for which a decision has been made not to restore or maintain sinus rhythm by any means, including catheter or surgical ablation. If a patient previously classified as having permanent AF is to undergo catheter or surgical ablation, the AF should be reclassified.

CONVENTIONAL AND NOVEL RISK FACTORS OF AF DEVELOPMENT AND PROGRESSION

The development and progression from paroxysmal to persistent and longstanding persistent AF has many risk factors[6]. Several conventional and novel risk factors have been proposed (Table 1).

AF begets AF

The most important predictor of AF progression is possibly AF itself[7]. At an early stage, AF determines an atrial electrophysiological, mechanical and structural atrial remodeling by shortening, mismatching and lengthening the atrial effective refractory periods (increase of dispersion) and by the depression of intra-atrial conduction and the loss of contractile function. The electrical, mechanical and structural remodeling determines the perpetuation of AF and the progression from paroxysmal to persistent and permanent forms. The longer one waits to initiate a rhythm treatment strategy, the more difficult it is to regain sinus rhythm. Dittrich *et al*[8] showed that patients who converted to sinus rhythm within 3 mo of onset of AF were more likely to maintain sinus rhythm at 6 mo than patients who converted more than 12 mo after onset of AF (67% *vs* 27%). By shortening the atrial refractory period, reducing conduction velocity and provoking contractile and structural remodeling, AF provokes AF[9].

Valvular heart disease

Almost any valvular lesion that leads to significant stenosis or regurgitation is associated with the development of AF. In patients with degenerative mitral regurgitation in sinus rhythm at diagnosis, the incidence of AF occurring under conservative management is high and similar whether the cause of mitral regurgitation is flail leaflet or simple mitral valve prolapse. After onset of AF,

Table 1 Conventional and novel risk factors for atrial fibrillation development and progression

Well-established risk factors
AF (AF begets AF)
Valvular heart disease
Hypertension
Coronary artery disease
Heart failure
Left atrial dilatation
Diabetes mellitus
Advancing age
Sex (male)
Congenital heart disease
Acute pericarditis
Hyperthyroidism
Alcohol consumption
Less-established risk factors
Obstructive pulmonary disease
Obstructive sleep apnea syndrome
Obesity
Left ventricular diastolic dysfunction
Atrial conduction delay (PR interval prolongation)
Genetic factors
Ethnicity
Emerging risk factors
Chronic kidney disease
Fibrosis
Inflammation
Elevated natriuretic peptides

AF: Atrial fibrillation.

an increased cardiac mortality and morbidity are both observed under conservative management[10]. Rheumatic heart disease is now uncommon in developed countries. It is, however, associated with high prevalence of AF. The highest frequency of AF in rheumatic heart disease occurs in those with mitral stenosis, mitral regurgitation, and tricuspid regurgitation in combination. AF, while occurring in 29% of patients with isolated mitral stenosis and in 16% with isolated mitral regurgitation, is an infrequent finding (1%) in patients with aortic valvular disease[11]. In addition, John *et al*[12] compared patients with mitral stenosis with 24 control patients. Patients with mitral stenosis showed, not only left atrial enlargement, but also a significantly reduced biatrial voltage (left atrium 1.8 + 0.6 mV *vs* 3.6 + 0.6 mV, right atrium 1.9 + 0.6 mV *vs* 3.3 + 0.5 mV), reduced conduction velocity, and prolonged effective refractory periods. These abnormalities may clearly play a role in the increased propensity to AF in patients with mitral stenosis.

Hypertensive heart disease

The association between hypertension and AF is well established. A history of hypertension increases 1.42-fold the risk of developing AF[13]. Although the increase in risk is relatively modest (relative risk, 1.2-1.5), the high prevalence of hypertension in the general population renders it the most significant population-attributable risk factor for AF beyond age and sex. It is observed that hypertension is responsible for 14% of all cases of AF[14]. Although overt systolic hypertension is strongly related with the progression of AF, recent studies demonstrated that systolic blood pressure in the prehypertensive range (130-139 mmHg) and widened pulse pressure are also associated with increased incidence of AF[15,16]. Mean arterial pressure does not seem to be related with AF.

Coronary artery disease

AF occurs transiently in 6%-10% of patients with acute myocardial infarction, presumably due to atrial ischemia or atrial stretching secondrary to HF[17]. These patients have a worse prognosis that is mostly due to comorbidities such as older age and HF. The Coronary Artery Surgical study which included 18000 patients showed that the incidence of AF is much lower (0.6%) in patients with chronic stable coronary artery disease (CAD)[16]. These patients probably had chronic AF; the prevalence of paroxysmal AF may be higher. AF was an independent predictor of increased mortality in patients with stable CAD[18]. Coronary artery disease can promote AF *via* multiple mechanisms. Myocardial infarction often causes substantial left ventricular dysfunction and HF predisposing to AF. Acute atrial ischemia/injury promotes AF by causing important atrial conduction disturbances, likely related to impaired cell-to-cell coupling[19]. Healed atrial infarctions and persistent ischemia enhances AF by causing Ca^{2+} - handling abnormalities, resulting in delayed afterdepolarizations and triggered activity resulting in ectopic firing, along with structural remodeling and reentry[20]. Chronic atrial coronary artery occlusion in conjunction with autonomic activity promotes ectopic firing and AF.

Age and sex

Aging is accompanied by atrial structural remodeling associated with substantial conduction abnormalities[21]. Gaborit *et al*[22] showed that men have greater expression of important repolarizing ion channel subunits, which could enhance atrial repolarization, shorten atrial refractoriness, and favor reentry. Moreover, men have greater left atrial dimensions that could promote AF maintenance[23].

Diabetes mellitus

Diabetes mellitus is an independent determinant of AF prevalence but predicted incidence only among women[24]. Over a mean follow-up of 7.2 years, diabetic patients without AF at baseline developed AF at an age/sex-adjusted rate of 9.1/1000 person-years, compared with 6.6/1000 person years among non-diabetic patients. Diabetes mellitus was associated with 26% increased risk of AF among women, but diabetes was not a statistically significant factor among men. Diabetes mellitus elicits AF *via* both structural remodeling, mediated by advanced glycosylation end products[25] and autonomic nervous system remodeling[26].

HF

AF and HF often occur together and each may predispose to the other. There is continuing controversy as to whether HF is merely a common coexisting condition among patients with AF or whether it is a true causative

factor. Among patients with HF, the prevalence of AF is variable, depending in part upon the severity of HF. The association is not limited to systolic left ventricular dysfunction but also AF is combined with diastolic dysfunction of the left ventricle[27]. Isolated diastolic dysfunction is associated with an increased AF incidence, possibly reflecting shared risk factors such as advancing age and hypertension. Although the association between AF and HF is well established, the causative relationship between the two has not been fully elucidated. Probably, AF can cause reductions in cardiac output (because of shorter diastolic filling time, loss of atrial contractile function, and elevated filling pressures) and tachycardia-induced cardiomyopathy[28]. HF results in structural and electrical remodeling changes that predispose to AF.

Hypertrophic cardiomyopathy

AF has been reported in 10%-28% of patients with hypertrophic cardiomyopathy (HCM)[29]. AF is the most common arrhythmia in patients with HCM. Olivotto *et al*[30] evaluated 480 patients with HCM with a mean follow-up of 9.1 years and found the prevalence of AF to be 22%. More recently, a study in Japan examined 261 patients with HCM and found that 74 (28%) patients had documented paroxysmal AF or permanent AF[31]. The high prevalence of AF in HCM is related to atrial dilation and remodeling in the setting of diastolic dysfunction, mitral regurgitation, and atrial fibrosis[30,31]. AF is an important prognostic indicator in patients with HCM, because these patients are typically at a higher New York Heart Association functional class and have a poorer outcome. This subgroup of patients with HCM is at an increased risk of cardiovascular morbidity and mortality in the form of thromboembolic events, HF, and sudden death[32]. In a systematic review, Kumar *et al*[33] reported that in HCM brain natriuretic peptide, left atrial size (left atrial volume measured with cardiac magnetic resonance), higher left atrial mean extent of late gadolinium enhancement in cardiac magnetic resonance, left ventricular myocardial fibrosis determined by delayed contrast enhancement, sleep apnea, longer *P*-wave duration, genetic factors, and ischemia are associated with AF progression.

Dilated cardiomyopathy

AF is common in patients with dilated cardiomyopathy (DCM). Epidemiologic studies have shown that 30%-40% of patients with left ventricular dysfunction and systolic HF from any cause will develop AF during the course of their disease, and AF has been associated with increased morbidity and mortality[34-36]. In experimental subjects, the increased incident of AF is associated with atrial structural abnormalities, with increased atrial fibrosis associated with slowing conduction of velocity and conduction heterogeneity[37]. In humans, Sanders *et al*[38] also showed that AF in patients with left ventricular dysfunction is associated with widespread areas of low voltage and electrical silence consistent with scar, and with regional atrial conduction slowing with prolongation of the *P*-wave duration, in addition to altered sinus node function. Pulmonary veins are responsible for arrhythmia initiation[39]. Atrial electrical and structural remodeling outside the pulmonary veins is the substrate of maintenance of persistent AF. Rotors, or high-frequency sources within the atrium, have been recently proposed as mechanisms for both initiation and maintenance of persistent AF[40].

Peripartum cardiomyopathy

In 2007, the European Society of Cardiology working group on myocardial and pericardial diseases redefined cardiomyopathies including peripartum cardiomyopathy (PPCM), which it is defined as a form of DCM that presents with signs of cardiac failure during the last month of pregnancy or within 5 mo of delivery[41]. Limited data regarding the association of PPCM and AF exist in the literature. Biteker *et al*[42] studied 42 women with PPCM. Five of them (11.9%) had AF and AF had no apparent effect on survival or recovery of left ventricular function. Kane *et al*[43] examined 33 women with PPCM and 1 (3%) of them had AF. Finally, Isezuo and Abubakar[44] showed that 2 out of 65 women (3.1%) developed AF strengthening the observation that PPCM is associated with AF.

Chronic kidney disease

AF is more prevalent in patients with chronic renal dysfunction (CRD). AF risk increases with severity of kidney dysfunction (HR of 1.3-1.6 and 1.6-3.2 with an estimated glomerular filtration rate of 30-59 and < 30 mL/min per 1.73 m^2, respectively, *vs* estimated glomerular filtration rate ≥ 60 mL/min per 1.73 m^2)[45]. These two entities (AF and CRD) share common associated factors such as coronary heart disease, HF, hypertension, left ventricular hypertrophy and systemic inflammation. In addition, macroalbuminuria and microalbuminuria were significantly associated with higher AF risk.

Sleep apnea and obesity

Accumulating data have demonstrated a clear and significant association between obstructive sleep apnea (OSA) and AF[46,47]. The occurrence of AF in 400 middle-aged patients who had moderate or severe OSA (apnea-hypopnea index ≥ 25) was more than 3%. Furthermore, twelve of the study patients who underwent tracheostomy, bypassing the obstructed airway, had complete elimination of AF up to 6 mo later, something that clearly shows the straight correlation between AF and OSA[46]. In the largest registry until now, Gami *et al*[47] showed that OSA and AF were significantly associated. Body mass index and the decrease in nocturnal oxygen saturation were independent predictors of AF. This study, also, proves the correlation between obesity and AF. Multiple pathophysiological pathways link OSA with AF. Increased left atrial size, hypertension and diastolic dysfunction may coexist in OSA and AF[48]. AF probably occurs as a complex interaction of several hemodynamic and sympathetic consequences of OSA.

These include autonomic dysregulation[49], elevated sympathetic tone, oxidative stresses, endothelial dysfunction, and left atrial stretch[50]. OSA is associated with systemic inflammation, increased levels of C-reactive protein (CRP), serum amyloid A, and interleukins[51]. These observations makes us believe that OSA and AF share common pathways, which contribute to atrial fibrosis and structural and electrical remodeling. Finally, Al Chekakie *et al*[52] showed that central obesity and pericardial fat is associated with AF. Pericardial adipose tissue contributes to inflammation and progression to AF. Patients with paroxysmal AF had significantly greater pericardial fat volume on average than patients in sinus rhythm (93.9 mL *vs* 76.1 mL) and the persistent AF patients had a significantly larger volume of pericardial fat volume on average than the paroxysmal AF patients (115.4 mL *vs* 93.9 mL).

Congenital heart disease

AF has been reported in approximately 20% of adults with an arial septal defect[53]. AF and atrial flutter also occurs in other forms of congenital heart disease that affect the atria, including Ebstein's anomaly[54] and patent ductus arteriosus[55], and after surgical correction of some other abnormalities, including ventricular septal defect, tetralogy of Fallot, pulmonary valve stenosis, and transposition of the great vessels.

Hyperthyroidism

Patients with hyperthyroidism have an increased risk of AF progression[56]. Frost *et al*[57] showed that among 40628 patients with clinical hyperthyroidism, 8.3% had AF or atrial flutter. Increased beta adrenergic tone play a crucial role for the development of AF in hyperthyroidism, often combined with rapid ventricular response. Furthermore, hyperthyroidism increases the likelihood of AF in experimental models, even in the presence of beta receptor and vagal blockade[58]. The pathophysiology remains unknown, but may be related to an increased automaticity and enhanced triggered activity of pulmonary vein cardiomyocytes[59]. The risk for development of AF is also increased in patients with subclinical hyperthyroidism[60,61]. It remains controversial whether patients with AF associated with previous treated thyrotoxicosis are at increased risk of thromboembolism, in the absence of other known risk factors[62].

Other clinical risk factors

AF is associated with a variety of other types of cardiopulmonary disease. AF is seen in 10% to 14% of patients with documented pulmonary embolism[63]. AF also occurs in chronic obstructive pulmonary disease[64], myocarditis[65] and acute pericarditis[66]. In addition, electrolytic disturbances like hypokalemia or low serum magnesium[67] initiates AF. Alcohol consumption contributes, also, to the development of AF[68]. Finally, prior surgery, especially and coronary artery bypass grafting[69] predispose to AF.

CLINICAL RISK SCORES FOR PREDICTION OF AF DEVELOPMENT AND PROGRESSION

The HATCH score [hypertension - age (75 years and older) - transient ischemic attack or stroke (2 points) - chronic obstructive pulmonary disease - HF (2 points)] allows an instant classification of the risk of progression to persistent or permanent AF in patients with paroxysmal AF[70]. de Vos *et al*[70] showed that nearly 50% of the patients with a HATCH score more than 5 progressed persistent AF, compared with only 6% of the patients with a HATCH score of 0. Malik *et al*[71] described LADS score [left atrial diameter (0-2 points), age (0-2 points), diagnosis of stroke (0-1 point), and smoking status currently (0-1 point)], a 6-point scoring system. A score of 4 or greater was associated with a sensitivity of 85.5% and a specificity of 53.1% for progression AF. CHADS2 score [one point each for age > 75 years, hypertension, diabetes and HF or low ejection fraction, and two points for history of prior stroke or transient ischemic attack (TIA)] and CHA2DS2-VASc score [congestive HF (1 point), hypertension (1 point), diabetes mellitus (1 point), history of stroke, TIA or thromboembolism (2 points), vascular disease (history of myocardial infarction, peripheral vascular disease or aortic atherosclerosis) (1 point), age 65-74 years old (1 point), age > 75 years old (2 points), sex male (0 points), female (1 point)] has been shown to be associated with post-ablation AF recurrences[5]. Letsas *et al*[72] examined 126 patients with symptomatic paroxysmal AF who underwent left atrial ablation. Over 16 mo, 89 patients were recurrence-free (70.6%). In the multivariate analysis, both CHADS2 and CHA2DS2-VASc score were independently associated with AF recurrence. Cut-off analysis showed that a score ≥ 2 for both CHADS2 and CHA2DS2-VASc scores showed the highest predictive value for AF recurrence.

BIOMARKERS FOR PREDICTION OF AF DEVELOPMENT AND PROGRESSION

Several biomarkers have been proposed as predictors of occurrence and progression of AF. Bruins *et al*[73] were the first to propose a direct link between inflammation and AF by observing an increased frequency of AF after coronary artery bypass surgery, where AF occurred on the second and third postoperative day coinciding with the peak elevation of CRP. CRP is an acute phase protein, which is directly related to inflammation. Raised levels of CRP have been noted to be higher among patients with AF when compared with patients in sinus rhythm[74]. Persistent AF patients have a higher CRP than paroxysmal AF patients, and both groups have a higher CRP than controls. Furthermore, CRP is considered as a significant predictor of early AF relapse after successful cardioversion, even after adjustment for multiple risk factors, such as hypertension and coronary artery disease[75]. Microalbuminuria combined with an elevated

CRP raises fourfold the risk of AF[76]. Korantzopoulos *et al*[77] presented data from a study of 30 AF patients undergoing cardioversion. Patients with arrhythmia relapse exhibited an increase in fibrinogen levels compared with those who remained in sinus rhythm. In addition, there was a trend to reduced CRP levels among those patients who were successfully cardioverted compared with those who relapsed. IL-6 plays a key role in inflammation and to the progression of AF. Gaudino *et al*[78] showed that a 174G/C polymorphism of the promoter of the *IL-6* gene appears to influence the development of postoperative AF supporting the role of inflammation in the development of postoperative AF. The importance of troponin, as a biomarker, in an AF population was first described in a substudy of RELY trial[79]. The results indicated that troponin Ⅰ levels ≥ 0.01 mg/L were seen in 55% of the 6189 patients with AF and at least one risk factor for stroke. Troponin was significantly and independently associated with increased risk of stroke, systemic embolism and cardiovascular death. These results were in concordance with the ARISTOTLE biomarker study where 14892 patients with AF were treated either with apixaban or warfarin in order to reduce the risk of stroke[80]. The ARISTOTLE troponin substudy results proved that the troponin levels were related to the risk of thrombo-embolic events and cardiovascular death. Other biomarkers which are increased in wall tension such as volume or pressure overload and are related with AF is B-type natriuretic peptide (BNP) and N-terminal fragment (NT-proBNP). Ellinor *et al*[81] first described that patients with AF had elevated levels of natriuretic peptides compared with matched controls in sinus rhythm. The levels of natriuretic peptides fall rapidly following restoration of sinus rhythm[82]. Patton *et al*[83] recently reported that elevated NT-proBNP levels predict an increased risk of development of AF independent of other risk factors including echocardiographic parameters. In addition, a substudy of the RELY trial showed that the level of NT-proBNP was associated with the risk of thrombo-embolic events and cardiovascular mortality[79]. Plasma D-dimer is a marker of fibrin turnover, and is used as an index of thrombogenesis. A substudy of the ARISTOTLE trial showed that D-dimer levels were a predictor of stroke, mortality and major bleeding[84].

IMAGING FOR PREDICTION OF AF DEVELOPMENT ANA PROGRESSION

Echocardiographic parameters

Left atrial size is a well-known predictor of AF development. A left atrial size greater than 4 cm has been associated with a significantly higher AF recurrence rate[85]. The left atrial volume measured by transthoracic echocardiography is possibly superior to left atrial diameter in predicting progression to persistent AF[86]. Li *et al*[87] reported that the E/e' index (E, early transmitral flow velocity; e', early diastolic mitral annular velocity), an index of diastolic dysfunction, was the best independent predictor of AF recurrence after catheter ablation. E/e' > 11.2 before ablation has been associated with AF recurrence. Shaikh *et al*[88] showed that speckle left atrial strain and stiffness index can predict the possibility of maintenance in sinus rhythm after cardioversion for AF. Changes in longitudinal left atrial strain (peak systolic longitudinal strain) after cardioversion were significantly higher among individuals who remained in sinus rhythm when compared to individuals with recurrent AF[88].

Magnetic resonance imaging and voltage mapping

Late gadolinium enhancement-magnetic resonance imaging (LGE-MRI) allows the direct visualization of atrial arrhythmic substrate. Vergara *et al*[89] described a new staging system for AF based on the amount of left atrial enhancement on LGE-MRI, the Utah score (Utah Ⅰ ≤ 5%, Utah Ⅱ > 5%-20%, Utah Ⅲ > 20%-35%, and Utah Ⅳ > 35%). On the basis of patient stage, a more tailored approach to AF management can be taken. Patients with a previous stroke had a significantly higher percentage of left atrial fibrosis compared with those without (24.4% ± 12.4% *vs* 16.1% ± 9.8%, $P \leq 0.001$). There was a significant difference in the rate of thromboembolism between patients with stage Ⅰ and those with stage Ⅳ of atrial remodeling as assessed by LGE-MRI. In addition patients with CHADS2 score ≥ 2 had higher amounts of left atrial fibrosis. The DECAAF study showed that left atrial fibrosis contributes to the progression of AF. The more fibrosis there is, the more likely the arrhythmia will persist following ablation[90]. Atrial fibrosis estimated by LGE-MRI in 260 AF patients, including 65% with paroxysmal AF, was a significant predictor of recurrence. Each 1% increase in fibrosis was associated with a 6% increased risk of recurrence. Fibrosis was categorized as stage 1 (< 10% of the atrial wall), 2 (≥ 10%-< 20%), 3 (≥ 20%-< 30%), and 4 (≥ 30%). At one year, 88% of patients with stage 1 fibrosis were free of AF. For those with stage 2, 3, or 4 fibrosis, 69%, 55%, and 45% were free of recurrence at one year, respectively. At 475 d, 86%, 64%, 51%, and 35% of those with stage 1, 2, 3, and 4 fibrosis were free of AF, respectively. Electroanatomic bipolar voltage mapping has proved to have great correlation with DE-MRI. Jadidi *et al*[91] have demonstrated bipolar voltages of 0.63 ± 0.8 in dense DE-CMRI areas, compared with 0.86 ± 0.89 in non DE-MRI areas. Moreover, Spragg *et al*[92] have demonstrated that the mean atrial voltage in areas identified as scar by DE-MRI was 0.39 ± 0.61 mV, while in areas identified as normal by DE-CMRI was 1.38 ± 1.23 mV.

There is now increasing evidence that even in patients with so-called lone or idiopathic AF, the AF is an arrhythmic manifestation of a structural atrial disease which has recently been defined and described as fibrotic atrial cardiomyopathy (FACM). Different expressions can be found from mild (FACM Ⅰ), moderate (FACM Ⅱ) to excessive fibrosis (FACM Ⅲ), and wide clinical variations from asymptomatic to multiple arrhythmic

manifestations (including AF, left and/or right atrial re-entrant tachycardia, sinus, and/or atrioventricular node disease)[93]. Fibrosis results from a broad range of factors related to AF inducing pathologies such as cell stretch, neurohumoral activation, oxidative stress, and possibly even AF itself[94]. Stiles *et al*[95] investigated 25 patients with "lone" AF, during an electrophysiological study after at least 7 d in sinus rhythm, and found slower conduction velocity, longer effective refractory periods, and significantly lower voltages (left atrium 1.7 + 0.7 mV *vs* 3.3 + 0.7 mV, right atrium 1.7 + 0.4 mV *vs* 2.9 + 0.4 mV) compared with control patients without AF. These findings confirm a substantial chronic structural biatrial substrate since the electrical remodelling is reversible within a few days. It might be that not all patients with paroxysmal "lone" AF have an underdetected chronic substrate, but many more than assumed. The debate is whether the fibrosis is causative or merely a result of AF. Several data suggest that fibrosis is causative and that AF-induced fibrosis may be part of the vicious cycle. In animal models, reversal or prevention of fibrosis prevents AF[96]. Furthermore, AF substrate in the absence of any cellular electrophysiological abnormalities has been demonstrated in a transgenic mouse model of isolated atrial fibrosis[97].

CONCLUSION

AF is a progressive disease associated with increased morbidity and mortality. Prevention of arrhythmia progression is therefore of paramount importance. An intense rhythm control strategy may be the first step towards this direction (sinus rhythm begets sinus rhythm). The modification of common risk factors of AF development and progression such as hypertension, obesity, and sleep apnoea should be additionally considered. Emerging risk factors such as inflammation and fibrosis will guide the therapeutic approach of AF in the future.

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MINIREVIEWS

Tilt table test today - state of the art

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Abstract

A tilt table test (TTT) is an inexpensive, noninvasive tool for the differential diagnosis of syncope and orthostatic intolerance and has good diagnostic yield. The autonomic system malfunction which underlines the reflex syncope is manifested as either hypotension or bradycardia, while an orthostatic challenge is applied. The timing of the response to the orthostatic challenge, as well as the predominant component of the response help to differentiate between various forms of neurocardiogenic syncope, orthostatic hypotension and non-cardiovascular conditions (*e.g.*, pseudosyncope). Medications, such as isoproterenol and nitrates, may increase TTT sensitivity. Sublingual nitrates are easiest to administer without the need of venous access. TTT can be combined with carotid sinus massage to evaluate carotid sinus hypersensitivity, which may not be present in supine position. TTT is not useful to access the response to treatment. Recently, implantable loop recorders (ILR) have been used to document cardioinhibitory reflex syncope, because pacemakers are beneficial in many of these patients, especially those over 45 years of age. The stepwise use of both TTT and ILR is a promising approach in these patients. Recently, TTT has been used for indications other than syncope, such as assessment of autonomic function in Parkinson's disease and its differentiation from multiple system atrophy.

Key words: Syncope; Orthostatic intolerance; Tilt table test; Hypotension; Bradycardia

Core tip: A tilt table test (TTT) is a noninvasive tool for the differential diagnosis of syncope and orthostatic intolerance. The way of the response to the orthostatic challenge helps to differentiate between various forms of neurocardiogenic syncope, orthostatic hypotension and non-cardiovascular conditions. TTT can be combined with carotid sinus massage to evaluate carotid sinus hypersensitivity, which may not be present in supine position. Implantable loop recorders (ILR) have been used to document cardioinhibitory reflex syncope. The stepwise use of both TTT and ILR is a promising approach. TTT has been used to assessment of autonomic function in Parkinson's disease.

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INTRODUCTION

The tilt table test (TTT) was initially described by Kenny *et al*[1] in 1986 as a tool to diagnose syncope of unknown origin. Since then various protocols have been developed. The cornerstone of the test is an orthostatic challenge which is done with the upright tilt. Apart from its main use in the syncope workup, use of the test was described in the evaluation of the presence of autonomic neuropathy in a variety of conditions[2,3]. The main idea behind the test is that reflex syncope is due to the abnormal cardiac autonomic reflexes, which lead to inappropriate vasodilatation (vaso-depressive reflex syncope), inappropriate bradycardia (cardio-inhibitory reflex syncope) or a mixed response[4-6]. A prolonged upright position is a known trigger of reflex syncope, where, after an initial normal adaptation to standing, inappropriate vasodilatation or bradycardia appears, leading to symptoms. This is different from the orthostatic hypotension, where the initial response to standing is abnormal.

DEFINITION OF DIFFERENT TYPES OF ORTHOSTATIC INTOLERANCE

European Society of Cardiology guidelines on diagnosis and management of syncope describe 6 major types of syndromes of orthostatic intolerance, which may cause syncope[7] and the tilt test is useful for making a correct diagnosis. Four of them are different types of orthostatic hypotension. The initial orthostatic hypotension (up to 30 s since postural challenge) is caused by the mismatch between cardiac output and systemic vascular resistance. It usually happens either in young, thin patients or in elderly patients treated with medications or with carotid sinus hypersensitivity and is usually manifested by the fall in blood pressure associated with dizziness in rare syncopal episodes. Classic orthostatic hypotension takes from 30 s to 3 min, is caused by autonomic failure to increase the systemic vascular resistance while standing, with the resultant pooling of blood in lower extremities and subsequent fall in blood pressure. Sometimes, significant volume depletion may cause this type of orthostatic intolerance, even when autonomic reflexes function normally. This form of orthostatic hypotension usually occurs in elderly patients, or in association with vasodilator or volume depleting medications, with orthostatic dizziness as a main manifestation and infrequent syncope. Delayed orthostatic hypotension occurs between 3 and 30 min, is caused by a progressive fall in venous return, low cardiac output and diminished reflex vasoconstriction; however, there is no decrease in heart rate. This type is present in elderly patients with autonomic failure, vasoactive medications and comorbidities. It is manifested by a prolonged prodrome of dizziness, weakness, visual disturbances, chest, neck and back pain, followed by rapid syncope. Reflex (vasovagal) syncope takes 3 to 45 min of postural challenge to develop. It is characterized by an initially normal adaptation reflex, followed by a rapid vasovagal reaction with reflex vasodilation and bradycardia. It is manifested by prodrome, which includes dizziness, nausea and sweating (some symptoms are caused by autonomic activation), always followed by syncope and mostly occurring in young female patients. Post exercise syncope, which happens in the first minute after cessation of intense physical activity, is now understood to be a form of reflex syncope[8,9]. When investigating the exercise related syncope, the initial effort should concentrate on excluding cardiac causes of syncope such as hypertrophic cardiomyopathy, valvular disease, or channelopathies.

Elderly patients with comorbidities may have a combination of delayed orthostatic hypotension with reflex syncope. Postural orthostatic tachycardia syndrome (POTS) is manifested by a significant increase in heart rate (an increase of more than 30 bpm or a heart rate of 120 bpm or more) during postural challenge without a fall in blood pressure (it can be quite variable). The mechanism of POTS is incompletely understood and is associated with physical deconditioning, and it usually happens in young females.

THE DIAGNOSTIC VALUE OF TTT

The etiology of reflex syncope can be divided into its common form (vasovagal - where postural challenge or emotion causes the abnormal reflex) and to the situational syncope (where this reaction is caused by a specific trigger). The autonomic malfunction causing reflex syncope is either a vasodepressive response (loss of sympathetic vasoconstrictive tone with resultant hypotension), cardioinhibitory response (active para-sympathetic stimulation with resultant bradycardia or asystole) or a mixed response. Carotid sinus hyper-sensitivity is a special form of reflex syncope.

Young patients are more prone to cardioinhibitory syncope, whereas older individuals are more likely to have a hypotensive response[10-12]. Moreover, an individual patient may demonstrate different types of responses on different occasions.

Normal individuals may have syncope during the tilt test (false positive result). However, comparing normal people who have a positive tilt test with people who have a history of reflex syncope[13] demonstrated that patients with a history of syncope had less time to syncope, a more rapid and persistent fall in blood pressure and higher peak serum epinephrine levels. False negative results have been reported with a rate of up to 30%, so a negative result does not exclude reflex syncope. Prolonged electrocardiographic monitoring may later diagnose cardioinhibitory syncope in tilt test negative patients[10,14]. There is no good gold standard for

evaluation of vasodepressive syncope.

The test is relatively simple and requires a special tilt table (a bed which rapidly moves the patient from a supine to an upright position, while the patient is secured to it with a foot board and restraints). Before the test, orthostatic hypotension is usually excluded. Electrocardiogram and blood pressure are continuously monitored (mostly by noninvasive measurements). Various protocols have been published with the differences mainly in the degree of tilt (60 to 90 degrees), its duration and use of pharmacological enhancement.

After monitoring of the patient in the supine position for 5 to 20 min (a longer duration is required if the intravenous cannula is used)[7], the patient is moved to the upright position and kept there for 20 to 45 min. If symptoms develop in association with bradycardia or hypotension, the test is considered positive. Obviously, the patient is rapidly returned to the supine position. If hypotension or bradycardia develops without symptoms, the test is suggestive of reflex syncope. Additionally, orthostatic hypotension may be documented.

If the test is negative, isoproterenol infusion (the dose is titrated to increase the average heart rate by 25%) or sublingual nitrates are used[15,16] during a second tilt. These are used to blunt the adaptive response of the autonomic nervous system and further unmask abnormal reflexes. Both were reported to have similar sensitivity (61%-69%) and specificity (92%-94%)[15,16]. Sublingual nitrates are easier to administer because venous access is unnecessary. However, one study demonstrated that in the pediatric population, administration of nitrates *vs* isoproterenol was associated with lower sensitivity (24% *vs* 56%) and more severe cardioinhibitory response[17]. A recent study which compared 2 protocols of sublingual nitrate administration (with and without a 5 min rest period in the supine position before nitroglycerin administration) found no differences with positive test in 61% *vs* 60% and specificity of 92% *vs* 90%, respectively[18]. This may eliminate the use of the rest period and shorten the test. Another study demonstrated that the use of the nitroglycerin tablet *vs* the sublingual spray is more specific, the latter form of usage was associated with higher rate of false positive response in both syncope patients and control patients[19]. Efremov *et al*[20] evaluated heart rate variability in patients with previous syncope who underwent a head up tilt test. Changes in the heart rate variability parameters between the first and last 5 min of the passive tilt test predicted syncope after nitroglycerine administration. Thus, evaluation of the heart rate variability during a tilt test may obviate the need for nitrate administration and shorten the test with decrease of side effects; however, this will require additional data processing.

Other triggers described during the tilt table testing are carotid sinus massage and clomipramine administration. Carotid massage in an upright position may demonstrate hypersensitivity, which may not be present in the supine position. Clomipramine is an serotonin selective reuptake inhibitor, which causes increased stimulation of serotonin receptors and, subsequently, diminishes sympathetic tone. One study[21] demonstrated an increased rate of positive response in patients (80% *vs* 53%) without increase in false positive responses.

Indications for the tilt table testing include recurrent unexplained syncope in patients without structural heart disease[7], or in patients with structural heart disease when cardiac causes have been excluded. Patients with a single episode of syncope do not usually need a tilt table test, unless there are specific circumstances associated with high risk (lifestyle or occupational hazard, *etc.*). Patients who are diagnosed with reflex syncope on the initial assessment are usually not candidates for the tilt test. The test may be useful to differentiate syncope with jerking movements from epilepsy[22,23]. Reflex syncope and epilepsy may actually coexist, so in some cases electroencephalogram recording during TTT may be of value[23]. Tilt test is also useful to differentiate reflex syncope from orthostatic hypotension[24], to evaluate a patient with recurrent falls[25] and to diagnose patients with psychogenic syncope[26]. In this scenario, syncope during the TTT will not be preceded by hypotension and/or bradycardia. The TTT is not used to evaluate the response to treatment. It is also not useful to evaluate patients with specific triggers which cause syncope.

One study[27] assessed neuro-autonomic evaluation in elderly patients with syncope which was determined to be likely to be neurally mediated after baseline initial evaluation. A diagnosis was made in 64% of cases with a diagnostic tilt test in 50%, carotid sinus massage (CSM) in 12% and orthostatic hypotension in 20%. The study demonstrated that neuro-autonomic evaluation is useful in elderly patients with syncope and that a tilt test was the most important contributor to this evaluation.

Another study[28] evaluated the diagnostic yield of tests in syncope according to the ICD-10 discharge diagnosis. The final diagnosis was reflex syncope in 21%, cardiac in 18%, orthostatic hypotension in 10%, others in 4% and unexplained in 48%. While the overall diagnostic yield of tests was low, the tilt test had a diagnostic yield of 47% during the initial admission and 61% during the work up.

A tilt test can be used to evaluate postural tachycardia syndrome. However, its performance is similar to the active standing test. One recent study[29] comparing TTT to active standing (blood pressure and heart rate at the 3rd and 9th minute) demonstrated no difference in the presence of orthostatic intolerance (P = 0.786). Syncope or presyncope was induced in 35% of patients in both groups. The only difference was a slight fall in blood pressure after 9 min of the tilt test but not in the active standing test. Another study[30] which compared the active standing test and the tilt test using heart rate measurements after 10 and 30 min found that an increase in 30 bpm in the upright position had good sensitivity with either method, but was less specific with the tilt test (40% *vs* 67% at 10 min and 20% *vs* 53% at 30 min, respectively). Thus, clinical features of orthostatic intolerance together with positive active standing are

Table 1 Comparison of relative merits of tilt table test and implantable loop recorders

	TTT	ILR
Advantages	Noninvasive, nonexpensive Differentiates between reflex syncope, orthostatic hypotension, carotid sinus hypersensitivity and pseudosyncope Assesses function of autonomic system	Reliable diagnosis of arrhythmias causing presyncope or syncope
Disadvantages	Significant false negative response (up to 30%) Pharmacological chellenge may be required	Invasive Cannot assess nonarrhythmic causes of syncope

TTT: Tilt table test; ILR: Implantable loop recorder.

probably sufficient for the diagnosis, while a tilt test is not going to be contributory in this situation.

COMPARISON WITH AN IMPLANTABLE LOOP RECORDER

Implantable loop recorder (ILR) provides continuous rhythm monitoring and can capture spontaneous episodes of cardioinhibitory syncope. ILR may more precisely determine a cause-effect relationship between bradyarrhythmia and syncope and exclude the tachyarrhythmic cause of syncope[31-33]. In case of cardioinhibitory syncope, TTT is more likely to demonstrate hypotension and bradycardia and less asystole, whereas ILR recordings during spontaneous episodes usually demonstrate asystole[10]. Thus, an implantable loop recorder may be used for the diagnosis of the suspected cardioinhibitory syncope instead of the tilt test. The drawback of this approach will be high proportion of implanted pacemakers in patients with documented spontaneous asystolic events, whereas patients with a positive tilt test will be mostly reassured about the benign nature of their disease. ISSUE 3 trial, reported in 2012[34] demonstrated high efficacy of dual chamber pacing with a rate drop response programing in patients who are 40 years and older with at least 3 previous syncopal episodes with ILR documented cardioinhibitory syncope (asystole for more than 3 s) or asystole for more than 6 s without syncope. In this randomized placebo-controlled (sensing only pacemaker) trial pacing caused 32% absolute and 57% relative reduction of syncopal episodes. According to this data, it seems prudent to proceed with ILR without a TTT in individuals with recurrent syncopal episodes of an unexplained nature, or with a suggested cardioinhibitory response. Of note, later analysis of this cohort of patients demonstrated that the benefit pacing in this group of patients was much greater in patients with negative TTT, than with positive one (the type of positive response was not significant)[35]. Another recent study[36] used an algorithm with carotid sinus massage, followed by a tilt test, and, if it is not diagnostic, ILR implantation. Asystolic response in any of the tests led to pacemaker implantation. The recurrence rate in the pacemaker-implanted patients (about half of the total group) was 9% in 1 year and 15% in 2 years (with no difference between CSM, TTT or ILR positive patients) and was significantly lower than in patients with nondiagnostic ILR (22% in 1 year and 37% in 2 years). The significance of prolonged asystole (> 30 s) was evaluated in one study[37]. A total of 2263 patients underwent TTT, 6.5% had an asystole, 11 patients (0.5%) had asystole between 30 and 63 s. Avoidance of triggers and physical counterpressure maneuvers were recommended in all patients, no one received a pacemaker. Although no patient died, 4 patients (36%) had recurrent syncopal episodes after a median follow-up of 42 mo. The summary of relative merits of TT *vs* ILR is shown in Table 1.

BEYOND SYNCOPE: THE USE OF TTT TO ASSESS AUTONOMIC NERVOUS SYSTEM IN DIFFERENT DISEASES

Besides its main use for differential diagnosis of syncope, TTT has been utilized in a variety of different disorders. Recent studies[38,39] used TTT in Parkinson disease. One study[37] demonstrated that in Parkinson's disease patients orthostatic hypotension is associated with a combination of decreased peripheral vascular resistance and inability to increase stroke volume, which means that autonomic dysfunction, involves both vasoregulatory dysfunction and cardiac denervation. Patients with preserved cardiac autonomic response (increase in stroke volume while in upright position) did not have orthostatic hypotension during TTT, despite reduction in peripheral vascular resistance. Orthostatic hypotension was very infrequent (1 in 46 patients) in patients who elevated peripheral vascular resistance during TTT. Another study[39] demonstrated that TTT is useful in making a differential diagnosis between multiple system atrophy (MSA) with predominant Parkinsonism and Parkinson's disease. Autonomic dysfunction was much more prevalent in MSA; combination of TTT and Valsalva maneuver having 91% sensitivity and 92% specificity. TTT also documented abnormal autonomic responses in patients with persistent post-concussion syndrome[40], restless leg syndrome[41] and anorexia nervosa[42].

CONCLUSION

TTT is a time proven test with good diagnostic yield for the diagnosis of syncope. Because of its relatively low cost and noninvasive nature, TTT can be widely used.

Combined with an implantable loop recorder, TTT will provide valuable information for the physician caring for patients with syncope. Apart from syncope, TTT demonstrated efficiency in evaluation of autonomic nervous system in noncardiac disorders.

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ORIGINAL ARTICLE

Clinical Trials Study

Clinical outcomes of combined flow-pressure drop measurements using newly developed diagnostic endpoint: Pressure drop coefficient in patients with coronary artery dysfunction

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Institutional review board statement: The study protocol was approved by the institutional review board at University of Cincinnati (UC) and the research and development committee at the Cincinnati Veteran Affairs Medical Center (CVAMC).

Clinical trial registration statement: The study was registered with Clinicaltrials.gov. The registration identification number is NCT01719016.

Informed consent statement: All study participants, provided informed written consent prior to the study enrolment.

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Data sharing statement: Technical details and statistical methods are available with the corresponding author at rupak.banerjee@uc.edu.

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Abstract

AIM: To combine pressure and flow parameter, pressure drop coefficient (CDP) will result in better clinical outcomes in comparison to the fractional flow reserve (FFR) group.

METHODS: To test this hypothesis, a comparison was made between the FFR < 0.75 and CDP > 27.9 groups in this study, for the major adverse cardiac events [major adverse cardiac events (MACE): Primary outcome] and patients' quality of life (secondary outcome). Further, a comparison was also made between the survival curves for the FFR < 0.75 and CDP > 27.9 groups. Two-tailed χ^2 test proportions were performed for the comparison of

primary and secondary outcomes. Kaplan-Meier survival analysis was performed to compare the survival curves of FFR < 0.75 and CDP > 27.9 groups (MedcalcV10.2, Mariakerke, Belgium). Results were considered statistically significant for $P < 0.05$.

RESULTS: The primary outcomes (%MACE) in the FFR < 0.75 group (20%, 4 out of 20) was not statistically different ($P = 0.24$) from the %MACE occurring in CDP > 27.9 group (8.57%, 2 out of 35). Noteworthy is the reduction in the %MACE in the CDP > 27.9 group, in comparison to the FFR < 0.75 group. Further, the secondary outcomes were not statistically significant between the FFR < 0.75 and CDP > 27.9 groups. Survival analysis results suggest that the survival time for the CDP > 27.9 group ($n = 35$) is significantly higher ($P = 0.048$) in comparison to the survival time for the FFR < 0.75 group ($n = 20$). The results remained similar for a FFR = 0.80 cut-off.

CONCLUSION: Based on the above, CDP could prove to be a better diagnostic end-point for clinical revascularization decision-making in the cardiac catheterization laboratories.

Key words: Pressure drop coefficient; Interventional cardiology; Intermediate coronary stenosis

Core tip: In the case of intermediate coronary stenosis, fractional flow reserve (FFR) is traditionally used as a functional end-point for interventional decision making in a cardiac catheterization laboratory. In this outcomes study, it was purported that pressure drop coefficient could prove to be a better clinical end-point for decision-making in comparison to the FFR.

Effat MA, Peelukhana SV, Banerjee RK. Clinical outcomes of combined flow-pressure drop measurements using newly developed diagnostic endpoint: Pressure drop coefficient in patients with coronary artery dysfunction. *World J Cardiol* 2016; 8(3): 283-292 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i3/283.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i3.283

INTRODUCTION

Accurate assessment of the severity of intermediate coronary stenosis is a clinical challenge to the interventional cardiologists. Quantitative anatomic tools have been proposed to address the issue but their relevance is still a matter of debate. Recently, the assessment of functional coronary lesion severity using sensor-equipped guidewires has emerged as a standard diagnostic modality to provide objective evidence of myocardial ischemia during cardiac catheterization[1,2]. Coronary diagnostic indices, fractional flow reserve (FFR; pressure derived), and coronary flow reserve (CFR; flow derived) showed a high agreement with non-invasive stress testing[3-5].

FFR (ratio of pressure distal to the stenosis to the pressure proximal to the stenosis) is the current gold standard for evaluating the functional significance of an epicardial stenosis[6-8]. FFR has a lower bound of "0", representing complete vessel obstruction and an upper bound of "1" represented no obstruction and normal flow. Based on extensive clinical outcomes trials, a cut-off value of 0.75[7] for FFR was shown to indicate hemodynamic significance of coronary stenosis in the presence of single vessel disease, and 0.80 for multi-vessel disease[9-13]. The limitations of FFR include the assumption of zero central venous pressure, and its dependence on achieving maximal hyperemia. Failure to achieve peak hyperemia may result in not achieving minimal constant microvascular resistance, leading to under estimation of pressure drop and over estimation of FFR across a stenosis[14].

The flow derived parameter CFR (ratio of flow at hyperemia to flow at rest) was found to have excellent agreement with noninvasive stress testing at a cut-off value of 2.0[3]. An abnormal CFR (< 2.0) corresponded to reversible myocardial perfusion defects with high sensitivity and specificity[3]. It should be noted that CFR provides the combined effect of epicardial stenosis and microvascular dysfunction, but cannot differentiate between the two. Hence, evaluation of epicardial coronary stenosis may not be accurate in the setting of microvascular dysfunction.

FFR and CFR are based on either intra coronary pressure or flow. Therefore, they can both be confounded by the presence of extended microvascular disease and cannot differentiate between hemodynamic status of the epicardial stenosis and microvasculature[15,16]. To overcome these limitations of FFR and CFR, hybrid pressure and velocity parameters were proposed. However, these parameters were defined for detection of either epicardial stenosis, namely, hyperemic stenosis resistance index (ratio of pressure drop across the stenosis to the distal velocity during hyperemia)[4]; or for the detection of microvascular dysfunction, namely, hyperemic microvascular resistance index (ratio of mean distal pressure and velocity during hyperemia)[17].

For simultaneous detection of epicardial stenosis and microvascular dysfunction using a single diagnostic parameter, we recently introduced the functional index, pressure drop coefficient (CDP); ratio of trans-stenotic pressure drop, Δp, to distal dynamic pressure, ($1/2 \times$ blood density $\times$ APV^2), where APV (average peak flow velocity) is measured under maximal hyperemia[18]. The CDP was validated *in vitro*[18,19], and *in vivo* animal studies[18-24] to differentiate between epicardial stenosis and microvascular dysfunction. In a recent pilot clinical study[25] CDP has been shown in a patient population to distinguish between degrees of stenosis severity. Further, for making interventional decisions, CDP > 27.9[26,27] was proposed as an indicator of significant epicardial stenosis, corresponding to a FFR < 0.75 cut-off in a single vessel.

Table 1 Summary of the characteristics of the 86 recruited patients

Variable		Study/group
Sex (M/F)		77/9
Age (yr)		61 ± 9
Ejection fraction (%)		58 ± 10
Clinical history		
	Diabetes	42/86
	Hypertension	70/86
	Dyslipidemia	60/86
	Previous myocardial infarction	21/86
	Smoking history	52/86
	Family history of CAD	23/86
	LV hypertrophy	4/86
Affected artery		
	LAD	43
	LCX	17
	RCA	26

M: Male; F: Female; CAD: Coronary artery disease; LV: Left ventricle; LAD: Left anterior descending; LCX: Left circumflex; RCA: Right coronary artery.

However, for the CDP to be included into regular clinical practice, the cut-off value CDP > 27.9 need to be associated with positive clinical outcomes. Hence, the objective of this pilot study is to compare the outcomes between the CDP > 27.9 and the clinical gold standard, FFR < 0.75. The hypothesis is that the combined pressure and flow parameter, CDP will result in better clinical outcomes in comparison to the FFR group. To test this hypothesis, a comparison was made between the FFR < 0.75 and CDP > 27.9 groups in this study, for the major adverse cardiac events [major adverse cardiac events (MACE): Primary outcome] and patients' condition (secondary outcome). Further, a comparison was also made between the survival curves for the FFR < 0.75 and CDP > 27.9 groups.

MATERIALS AND METHODS

Study patients

The protocol[25] was approved by the institutional review board at University of Cincinnati (UC) and Cincinnati Veteran Affairs Medical Center (CVAMC), and informed consent was obtained from all the participants. Patients who underwent exercise testing and myocardial perfusion scans were consented based on the inclusion and exclusion criteria, as explained below. The study was registered with Clinicaltrials.gov, with the identifier NCT01719016.

The study population consisted of 86 patients enrolled at the UC and CVAMC. Table 1 summarizes the clinical characteristics of the enrolled patients. The inclusion criteria for the study were: (1) chest pain; (2) abnormal stress test; (3) an angiographically detectable stenosis of moderate severity (defined as approximately 50% by visual examination) in a major coronary artery; and (4) left ventricular ejection fraction > 25%. Patients were excluded if they had: (1) left ventricular ejection fraction < 25%; (2) non-dialysis dependent chronic kidney disease with baseline serum creatinine greater than 2.5 g/dL; (3) history of type-Ⅱ heparin induced thrombocytopenia; (4) ostial lesions, serial stenoses, significant left main stenosis; (5) significant co-morbid conditions that would make coronary angiography prohibitive and contraindicated; and (6) pregnant women.

Cardiac catheterization and hemodynamic measurement

Using standard-of-care catheterization techniques, vascular access was through the femoral approach; a 5-to-6-French catheter was introduced into the femoral sheath and advanced into the ostium of the coronary artery. Unfractionated heparin was administered using a weight-based protocol. Aortic pressure was measured through the guiding catheter. Intra coronary pressure and flow measurements were obtained across the lesions either by using a 0.014-inch-diameter guidewire (Combowire, Volcano Corporation, California, United States) that combines a standard Doppler sensor at the tip and a standard pressure sensor 1.5 cm proximal to the tip or by 0.014-inch-diameter pressure and Doppler guide wires separately. The Combowire (or pressure wire) was set at zero, calibrated, advanced through the guiding catheter and normalized to aortic pressure before insertion into the target vessel. The wire was positioned distal to the stenosis in the target vessel, with the pressure transducer at least 30 mm distal to lesion. The position of the Doppler sensor was manipulated until an optimal and stable blood velocity signal was obtained. Adenosine was then infused intravenously (140 μg/kg per minute)[25] or *via* intracoronary (20 μg for the right coronary artery and 40 μg for the left coronary artery)[28] to induce maximal coronary blood flow. Aortic pressure (P_a), coronary pressure (P_d) and average peak velocity (APV) distal to the stenosis were recorded. All signals were continuously recorded at rest and throughout induction and decline of maximum hyperemia.

CDP calculation

Percent diameter stenosis, reference diameter, and minimal lumen diameter were obtained by quantitative analysis of coronary angiograms, with the use of a validated automated contour detection algorithm (Centricity Cardiology, GE Healthcare). CDP[18,20-22,24,27] is defined as the ratio of trans-stenotic pressure drop ($\Delta P = P_a - P_d$) to distal dynamic pressure. The product of blood density (ρ), the square of APV and a constant value of 0.5, *i.e.*, $0.5 \times \rho \times APV^2$, is calculated to obtain distal dynamic pressure, measured at hyperemia. Blood density, ρ does not change significantly at hyperemia, and thus can be assumed to have a constant value (1.05 g/cm^3)[20,29].

$CDP = \Delta P/(0.5 \times \gamma \times APV^2)$(a dimensionless parameter; where $\Delta P = P_a - P_d$), P_a and P_d are mean pressures measured proximal and distal to the stenosis at hyperemia, respectively.

Patient follow-up and study endpoints

All the patients were followed-up through either chart review, a phone call, and/or a questionnaire. The period

Table 2 Summary of the primary and secondary outcomes at a minimum of 1-year follow-up period

Variable		FFR < 0.75	FFR > 0.75	CDP > 27.9	CDP < 27.9	FFR < 0.80	FFR > 0.80	CDP < 25.4	CDP > 25.4
Primary outcome	Composite of MACE								
	All-cause mortality	3/20	2/66	2/35	3/51	4/35	1/51	3/47	2/39
	Myocardial infarction	1/20	1/66	0/35	2/51	2/35	0/51	1/47	1/39
	Revascularization	0/20	1/66	0/35	1/52	1/35	0/51	1/47	0/39
Secondary outcome: All questions related to patients' condition after the procedure	Q1: Health condition	7/20	1/66	7/35	1/51	7/35	1/51	7/47	1/39
	Q2: Heart attack	0/20	0/66	0/35	0/51	0/35	0/51	0/47	0/39
	Q3: Chest pain requiring medication	6/20	6/66	7/35	5/51	6/35	6/51	7/47	5/39
	Q4: Interventional procedure	5/20	3/66	4/35	4/51	5/35	3/51	4/47	4/39
	Q5: Re-hospitalization due to cardiac condition	2/20	5/66	4/35	3/51	2/35	5/51	4/47	3/39

MACE: Major adverse cardiac events; FFR: Fractional flow reserve; CDP: Pressure drop coefficient.

of follow-up was a minimum of 1 year. Through the follow-up, the primary outcomes, consisting of MACE, were determined. MACE was defined as the composite of all-cause mortality, myocardial infarction (MI), and repeat revascularization (Table 2).

The secondary outcomes consisting of patients' condition were determined through follow-up questionnaire based on 5 questions (Table 2). Q1: How has your health condition been after procedure? Q2: Have you been diagnosed of heart attack after procedure? Q3: Have you been experiencing chest pain requiring you to take nitroglycerin, since you had the procedure? Q4: Did you have any interventional procedure done after cardiac catheterization? Q5: Have you been re-hospitalized for cardiac-condition after this cardiac procedure? The answers to these questions comprised of the secondary outcomes.

Statistical analysis

The authors had prior biostatistics background, as apparent from previous publications[13,14,17-19]. Any patient lost to follow-up was counted as censored data. The data was segregated based on the cut-off value of FFR < 0.75 and FFR < 0.80 for significant epicardial stenosis. Similarly, for corresponding significant epicardial stenosis, CDP > 27.9 and CDP > 25.4[26,27] were used as the cut-off value. For the primary outcome analysis, the %MACE in the FFR < 0.75 (n = 20) group were quantified and compared against the %MACE in corresponding CDP > 27.9 (n = 39) group. Similar comparisons were also performed between the %MACE in the FFR > 0.75 (n = 66) and CDP < 27.9 (n = 47) groups. The same analysis were also performed for FFR = 0.80 and CDP = 25.4 groups.

For the secondary outcome analysis, the responses to the five questions (please see above) were quantified as percentages and compared between the FFR and CDP groups. For Q1, the number of patients answering "not feeling well" was counted. For Q3, Q4 and Q5, any patient answering "Yes" was counted. Q2 was excluded from presentation since there were no patients diagnosed with heart attack. All the comparisons were performed using a two-tailed χ^2 test with Yates correction. As a double check, comparisons were also performed using Fisher's exact test.

Further, survival analysis was also performed to assess the performance of CDP against FFR. The time between the index procedure and the time when the patient was last contacted (last follow-up) was recorded. Any patient who reached the primary outcome (%MACE) was counted as positive. Any patient lost to follow-up or who didn't reach the outcome was entered as censored data. Based on this, Kaplan-Meier survival analysis was performed. A comparison between the survival curves for the two groups was also performed using log-rank test. All the analyses were performed using MedCalc (V10.2, Mariakerke, Belgium). Results were considered statistically significant for $P < 0.05$.

RESULTS

In order to test the effectiveness of CDP cut-off (CDP > 27.9 and CDP > 25.4) as a guide for intervention decisions, the primary and secondary outcomes in patients were quantified and compared against the FFR cut-off (FFR < 0.75 and FFR < 0.80). In addition, survival curves were also generated and compared between the groups. These results are summarized below.

Primary outcome comparison between CDP and FFR

A comparison of the %MACE between the FFR < 0.75 and CDP > 27.9 groups, and FFR > 0.75 and CDP < 27.9

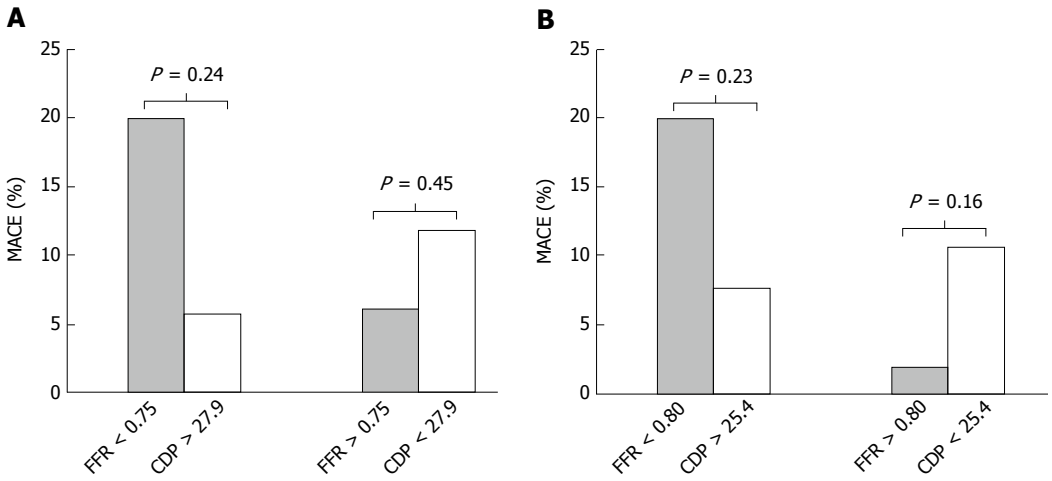

Figure 1 Comparison of % major adverse cardiac events in fractional flow reserve and pressure drop coefficient groups. MACE: Major adverse cardiac events; FFR: Fractional flow reserve; CDP: Pressure drop coefficient.

groups is summarized in Figure 1A. The %MACE in the FFR < 0.75 group (20%, 4 out of 20) was not statistically different (P = 0.24) from the %MACE occurring in CDP > 27.9 group (8.57%, 2 out of 35). Noteworthy is the reduction in the %MACE in the CDP > 27.9 group, in comparison to the FFR < 0.75 group. If a CDP-based strategy were to be implemented, the %MACE in this group would be lower (8.57%) in comparison to the FFR-guided strategy group (%MACE = 20%).

Similarly, the %MACE in FFR > 0.75 group was 6.06% (4 out of 66). This value was not statistically significant (P = 0.45) in comparison to a %MACE in the CDP < 27.9 group (11.76%, 6 out of 51).

Similar comparisons for FFR = 0.80 and CDP = 25.4 groups are presented in Figure 1B. The %MACE in the FFR < 0.80 group (20%, 7 out of 35) was not statistically different (P = 0.23) from the %MACE occurring in CDP > 25.4 group (7.69%, 3 out of 39).

Similarly, the %MACE in FFR > 0.80 group was 1.96% (1 out of 51). This value was not statistically significant (P = 0.16) in comparison to a %MACE in the CDP < 25.4 group (10.64%, 5 out of 47).

Secondary outcome comparison between CDP and FFR

The secondary outcomes, quantified through responses of the patients through follow-up questionnaire were also compared between the FFR < 0.75 and CDP > 27.9 groups, and also between the FFR > 0.75 and CDP < 27.9 groups. These results are summarized in Figures 2A and 2B, respectively.

Figure 2A summarizes the comparison between the FFR < 0.75 and CDP > 27.9 groups. In the FFR < 0.75 group patients not feeling well (Q1: 35%, 7/20) was not statistically significant (P = 0.36) in comparison to the slightly lower % of patients not feeling well in the CDP > 27.9 group (20%, 7/35). Similarly, the % of patients answering "Yes" to Q3, Q4, Q5 in the FFR < 0.75 group (Q3: 30%, 6/20; Q4: 25%, 5/20; Q5: 10%, 2/20) was not statistically different (Figure 2A) in comparison to the CDP > 27.9 group (Q3: 20%, 7/35; Q4: 11.43%, 4/35; Q5: 11.43%, 4/35).

In the FFR > 0.75 group (Figure 2B) patients not feeling well (Q1: 1.51%, 1/66) was not statistically significant (P = 0.59) in comparison to the % of patients not feeling well in the CDP < 27.9 group (1.96%, 1/51). Similarly, the % of patients answering "Yes" to Q3, Q4, Q5 in the FFR < 0.75 group (Q3: 9.09%, 6/66; Q4: 4.54%, 3/66; Q5: 7.58%, 5/66) was not statistically different (Figure 2B) in comparison to the CDP < 27.9 group (Q3: 9.8%, 5/51; Q4: 7.84%, 4/51; Q5: 5.88%, 3/51).

Figure 2C summarizes the comparison between the FFR < 0.80 and CDP > 25.4 groups. In the FFR < 0.80 group patients not feeling well (Q1: 20%, 7/35) was not statistically significant (P = 0.94) in comparison to the CDP > 25.4 group (17.95%, 7/39). Similarly, the % of patients answering "Yes" to Q3, Q4, Q5 in the FFR < 0.75 group (Q3: 17.14%, 6/35; Q4: 14.29%, 5/35; Q5: 5.71%, 2/35) was not statistically different (Figure 2A) in comparison to the CDP > 27.9 group (Q3: 17.95%, 7/39; Q4: 10.26%, 4/39; Q5: 10.26%, 4/39).

In the FFR > 0.80 group (Figure 2D) patients not feeling well (Q1: 1.96%, 1/51) was not statistically significant (P = 0.47) in comparison to the % of patients not feeling well in the CDP < 25.4 group (2.13%, 1/47). Similarly, the % of patients answering "Yes" to Q3, Q4, Q5 in the FFR < 0.80 group (Q3: 11.76%, 6/51; Q4: 5.88%, 3/51; Q5: 9.80%, 5/51) was not statistically different (Figure 2D) in comparison to the CDP < 25.4 group (Q3: 10.64%, 5/47; Q4: 8.51%, 4/47; Q5: 6.38%, 3/47).

Survival analysis

The Kaplan-Meier survival curves for the FFR < 0.75 and CDP > 27.9 groups were presented in Figure 3A. The results suggest that the survival time for the CDP > 27.9 group (n = 35) is significant (P = 0.048) in comparison to the survival time for the FFR < 0.75 group (n = 20).

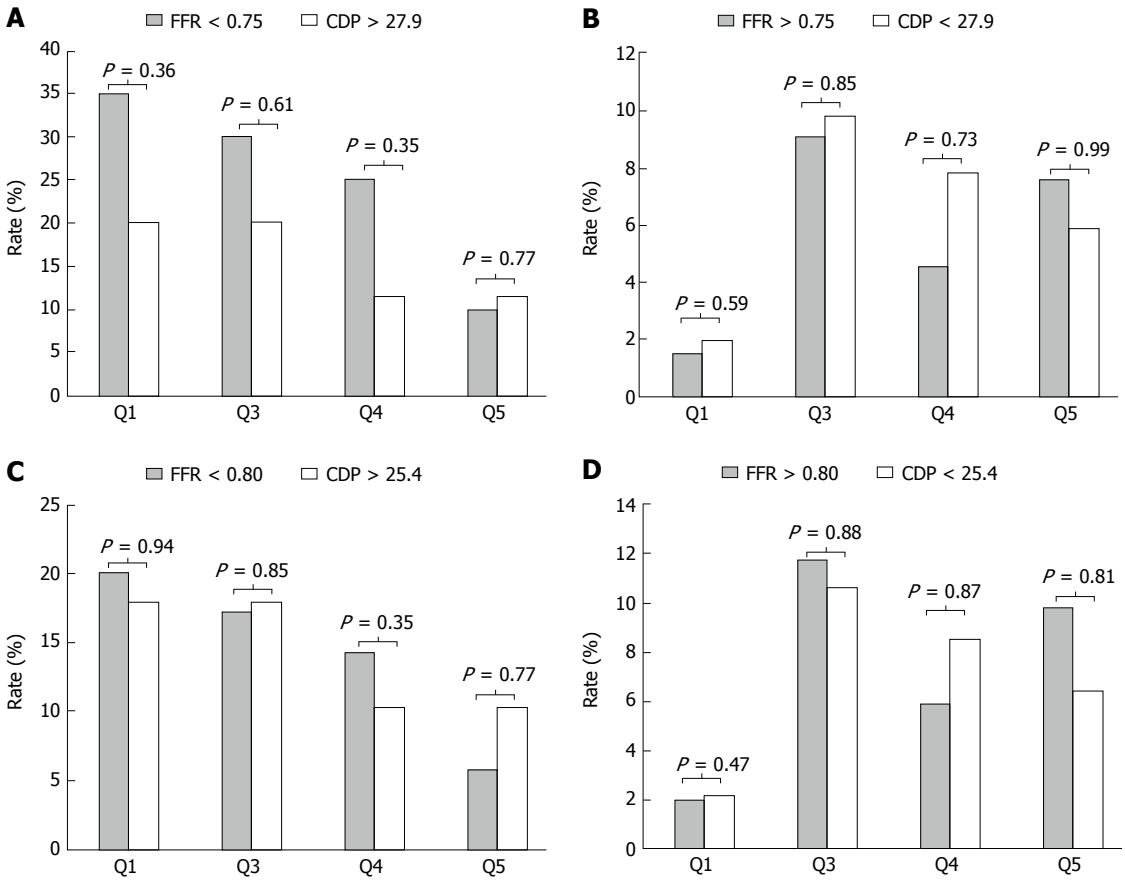

Figure 2 Comparison of patient conditions between fractional flow reserve and pressure drop coefficient groups at follow-up. A: FFR < 0.75 and CDP > 27.9; B: FFR > 0.75 and CDP < 27.9; C: FFR < 0.80 and CDP > 25.4; D: FFR > 0.80 and CDP < 25.4. FFR: Fractional flow reserve; CDP: Pressure drop coefficient.

Further, the hazard ratio between the two groups is 0.22 (95%CI: 0.06-1.24). This means that the survival expectancy in the FFR < 0.75 group is 0.22 times the survival probability in the CDP > 27.9 group. Similar results for FFR < 0.80 and CDP > 25.4 groups are presented in Figure 3B. The survival time for the CDP > 25.4 group (n = 39) is marginally significant (P = 0.066) in comparison to the survival time for the FFR < 0.80 group (n = 35).

The Kaplan-Meier survival curves for the FFR > 0.75 and CDP < 27.9 groups were presented in Figure 3C. The results suggest that the survival time for the CDP < 27.9 group (n = 51) is not significantly different (P = 0.29) in comparison to the survival time for the FFR > 0.75 group (n = 66). Further, the hazard ratio between the two groups is 1.95 (95%CI: 0.56-6.82). Similar results for FFR > 0.80 and CDP < 25.4 groups are presented in Figure 3D. The survival time for the CDP < 25.4 group (n = 47) is not significant (P = 0.094) in comparison to the survival time for the FFR > 0.80 group (n = 51).

DISCUSSION

The theoretical advantages of using a single physiological parameter that incorporates both pressure and flow measurements is well supported by ample evidence. However, the question remains whether this consideration is relevant in a clinical setting. The results of this study suggest that if clinical practice making strategy is based on CDP instead of FFR, there would be a significant increase in event free survival. Additionally, comparing patients who had CDP > 27.9 to FFR < 0.75 and CDP > 25.4 with FFR < 0.80 resulted in a trend towards reduced MACE and improved quality of life. Similar results were observed for FFR = 0.80 cut-off, with a corresponding CDP cut-off of 25.4. Purportedly the difference in clinical outcomes seen in this study reflects an enhanced accuracy in predicting ischemia.

CDP, defined as coronary trans-lesional pressure drop (Δp) to distal dynamic pressure ($0.5 \times \rho \times APV^2$) uses both pressure and flow measurements to assess stenosis severity. Additionally, it has the advantage of being a non-dimensional parameter based on fundamental fluid dynamics principles. It has been shown that coronary pressure drop (Δp) - flow relationship in a stenosed vessel is non-linear and can be described by $\Delta P = aV + BV^2$, where a and b are stenosis specific constants and V is the velocity. The Δp includes (a) viscous loss, a linear relationship of Δp and flow (or velocity), resulting from the friction between the blood flow and the lumen of the stenosis wall; and (b) loss due to the momentum change, a quadratic relationship of Δp and velocity, caused by the area change due to the stenosis.

FFR and CFR are affected in opposite directions by

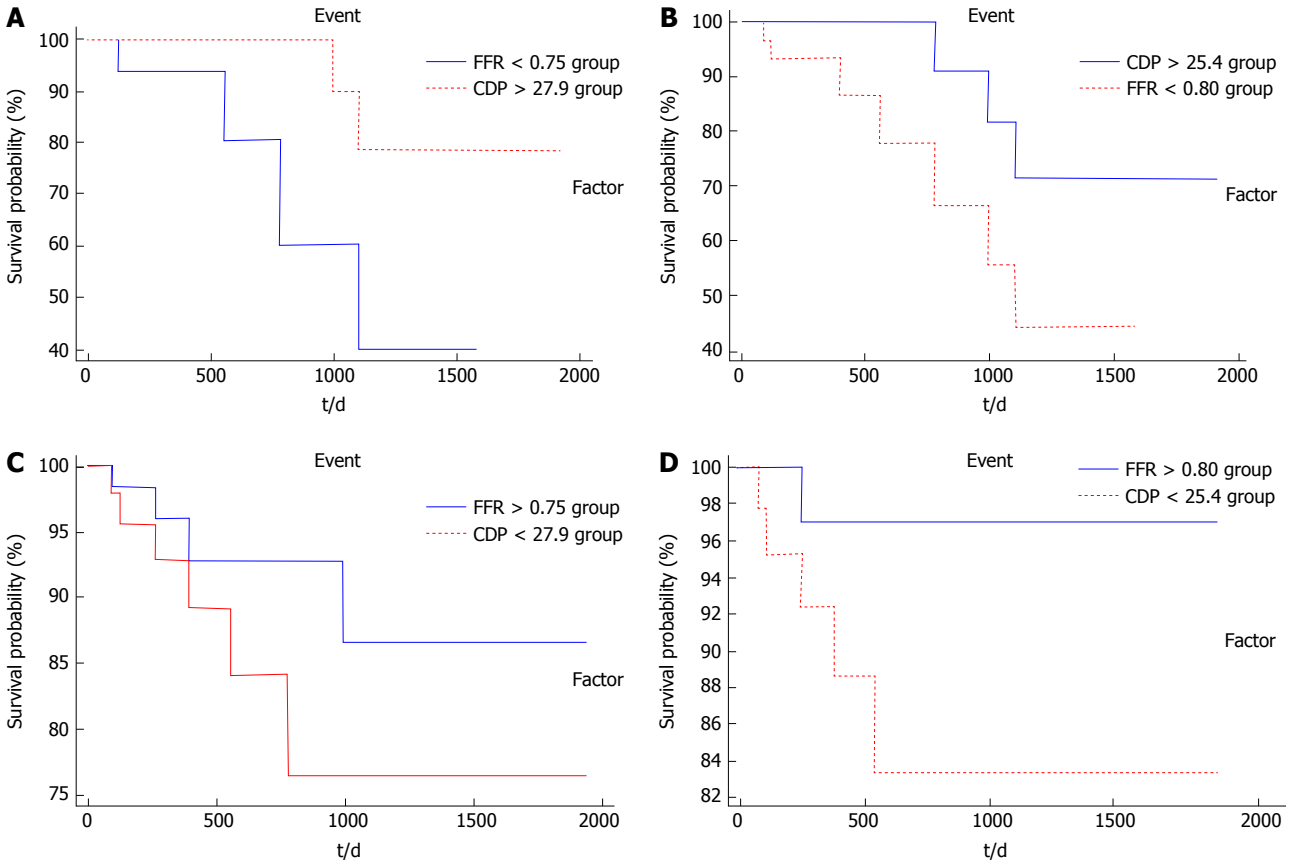

Figure 3 Survival curves. A: FFR < 0.75 and CDP > 27.9 groups (P = 0.048); B: FFR < 0.80 and CDP > 25.4 (P = 0.066); C: FFR > 0.75 and CDP < 27.9 groups (P = 0.29); D: FFR > 0.80 and CDP < 25.4 (P = 0.09). FFR: Fractional flow reserve; CDP: Pressure drop coefficient.

microvascular resistance, and assessment of ischemia by measuring FFR and CFR in the same coronary vasculature may yield discordant results in up to 40% of the cases[30]. This can be explained by the presence of diffuse epicardial disease which would lower CFR without significant impact on FFR. Conversely, a well preserved microvascular auto regulatory function may maintain CFR above the ischemic threshold while FFR is abnormal. In the presence of such conditions as diffuse lesion or concomitant microvascular disease, the complex interaction between pressure and flow might not be sufficiently explained by FFR or CFR alone, as FFR is a pressure-derived parameter and CFR is a flow-derived parameter. On the other hand, CDP combines both the pressure and flow in a single parameter and thus can distinguish between epicardial stenosis and microvascular dysfunction[22,26].

As previously mentioned, both FFR and CFR depend critically on the achievement of maximal hyperemia. Failure to achieve peak hyperemia may result in not achieving minimal constant microvascular resistance leading to under estimation of pressure drop and over estimation of FFR across a stenosis[11]. It should be noted that in the presence of microvascular dysfunction and submaximal hyperemia, pressure drop, and blood flow are affected in the same direction. Physiologically, the extent of reduction in maximal hyperemic flow due to microvascular dysfunction is higher than that due to epicardial stenosis[20]. In such circumstances, the square of maximal hyperemic flow in the denominator of CDP significantly accounts for this reduction, thus providing an increased resolving power for CDP for accurate evaluation of the status of epicardial stenosis.

Given these advantages of CDP, we believe that it can potentially have a significant role in clinical practice. However, it should be noted that the utilization of dual sensor wires for diagnostic purposes has not gained sufficient traction in cardiac catheterization laboratories partly because of the added complexity in acquiring functional data. Nevertheless, as the evidence from clinical outcome studies evolves and the technology advances further in making the dual sensor wires more steerable, less expensive and easier to use, the employment of these sophisticated concepts will be more tenable for use and application in the cardiac catheterization laboratory.

Several studies have confirmed the clinical utility of FFR in applying a "functional" PCI approach for the treatment of coronary stenosis, *i.e.,* to only revascularize the angiographic lesions that show significant FFR while deferring others. The DEFER study[11] comprised of 181 patients with stable ischemic heart disease and intermediate coronary stenosis. FFR > 0.75 was used to defer PCI and follow medical therapy in the deferred arm. At 5-year follow-up, the rate of MI or death was

significantly lower in the deferred group in comparison to the PCI group. The FAME trial[13] randomized 1005 patients to either FFR guided PCI or angiography guided PCI. The primary endpoint of MACE (MI, death, or repeat revascularization) at one year was significantly lower in the FFR guided strategy (13.2% *vs* 18.3%, $P = 0.02$).

To compare the outcomes between FFR guided PCI and optimal medical therapy alone, FAME 2[31], randomized 888 patients. The study was terminated early due to a significant difference in the primary endpoint of MACE in favor of the FFR guided strategy.

The results of these studies validate the role of FFR in guiding the clinical decision for management of coronary artery disease. Further, our study is purporting an improved accuracy for CDP over FFR in predicting major ischemic events as well as angina free survival. The reported outcomes from our analysis support the value of using CDP to make decisions regarding deferment of revascularization in clinical practice. Although statistical significance was not reached on most endpoints, the trends were robustly consistent throughout the spectrum of outcome follow-ups. Further validation in a larger cohort and a longer follow-up period may yield a stronger difference in support of CDP.

Limitations

In this study, all the clinical decisions were made on the basis of FFR only. Thus, using a larger sample size, a prospective randomized clinical trial of FFR *vs* CDP is needed to further investigate the clinical performance of CDP relative to FFR and validate the outcomes from this exploratory study.

In conclusion, in this pilot study, the primary (%MACE) and secondary (improved quality of life) outcomes between the FFR < 0.75 and CDP > 27.9 groups were compared. The %MACE in the CDP < 27.9 groups were slightly lower in comparison to the FFR < 0.75 group. However, this comparison was not statistically significant. Similarly, the secondary outcomes were not different between the FFR < 0.75 and CDP > 27.9 groups.

The event free survival in the CDP < 27.9 group was significantly ($P = 0.048$) higher in comparison the survival time in FFR < 0.75 group. Based on these, CDP could prove to be a good clinical endpoint for revascularization decision-making in a catheterization laboratory.

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COMMENTS

Background

Accurate assessment of the severity of intermediate coronary stenosis is a clinical challenge to the interventional cardiologists. Quantitative anatomic tools have been proposed to address the issue but their relevance is still a matter of debate. Hence, functional assessment of coronary lesion severity using sensor-equipped guidewires has emerged as a standard diagnostic modality to provide objective evidence of myocardial ischemia during cardiac catheterization.

Research frontiers

Pressure based parameter, fractional flow reserve (FFR) is currently being used as a clinical diagnostic marker for coronary interventions. A value of FFR < 0.80 is indicative of functionally significant coronary blockage, while a FFR > 0.80 indicates deferral of intervention to a later time. The applicability of FFR for intermediate stenosis intervention decision-making, in the presence of concomitant microvascular disease is an active research area.

Innovations and breakthroughs

This study proposes the newly developed diagnostic parameters, pressure drop coefficient (CDP), defined based on fundamental fluid dynamics. CDP combines both pressure and flow readings for interventional decision-making. Hence, it might prove to be a better parameter resulting in improved patient outcomes, as shown in this exploratory study.

Applications

The parameter CDP could be used for interventional decision-making in a cardiac catheterization laboratory, particularly in the presence of an intermediate coronary stenosis.

Peer-review

This is a nicely written article focusing on the clinical significance of different and combined flow-pressure drop measurements in coronary artery disease patients. The study is well planned and documented.

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Typical rise and fall of troponin in (peri-procedural) myocardial infarction: A systematic review

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Abstract

AIM: To identify the typical shape of the rise and fall curve of troponin (Tn) following the different types of myocardial infarction (MI).

METHODS: We conducted a systematic search in PubMed and Embase including all studies which focused on the kinetics of Tn in MI type 1, type 4 and type 5. Tn levels were standardized using the 99th percentile, a pooled mean with 95%CI was calculated from the weighted means for each time point until 72 h.

RESULTS: A total of 34 of the 2528 studies identified in the systematic search were included. The maximum peak level of the Tn was seen after 6 h after successful reperfusion of an acute MI, after 12 h for type 1 MI and after 72 h for type 5 MI. In type 1 MI there were additional smaller peaks at 1 h and at 24 h. After successful reperfusion of an acute MI there was a second peak at 24 h. There was not enough data available to analyze the Tn release after MI associated with percutaneous coronary intervention (type 4).

CONCLUSION: The typical rise and fall of Tn is different for type 1 MI, successful reperfusion of an acute MI and type 5 MI, with different timing of the peak levels and different slopes of the fall phase.

Key words: Troponin; Myocardial infarction; Systematic review; Reperfusion; Coronary artery bypass grafting

Core tip: In this systematic review we aimed to identify the typical rise and fall of cardiac troponin (Tn) in the different types of myocardial infarction (MI). A total of 34 of the 2528 studies identified in the systematic search were included. The typical rise and fall of Tn is different for type 1 MI, successful reperfusion of an

acute MI and type 5 MI, with different timing of the peak levels and different slopes of the fall phase.

van Beek D, van Zaane B, Looije M, Peelen L, van Klei W. Typical rise and fall of troponin in (peri-procedural) myocardial infarction: A systematic review. *World J Cardiol* 2016; 8(3): 293-301 Available from: URL: http://www.wjgnet.com/1949-8462/full/v8/i3/293.htm DOI: http://dx.doi.org/10.4330/wjc.v8.i3.293

INTRODUCTION

Myocardial infarction (MI) is the collective term for myocardial necrosis in the setting of myocardial ischemia[1]. There are many different conditions which can result in myocardial ischemia and subsequent MI. Currently, there are five distinct types of MI defined: Type 1 spontaneous MI related to atherosclerotic plaque rupture, type 2 MI secondary to an imbalance between oxygen supply and oxygen demand, type 3 MI resulting in death when biomarkers are not available, type 4a MI related to percutaneous coronary intervention (PCI), type 4b MI related to stent thrombosis, and type 5 MI related to coronary artery bypass grafting (CABG)[1].

For all different types of MI, excluding type 3, cardiac biomarkers are the cornerstone for diagnosing its occurrence. The preferred cardiac biomarker for the detection of myocardial damage is troponin (Tn)[1]. Tn (subtypes I en T) is part of the contractile apparatus of myocardial cells only and is therefore a highly specific biomarker for myocardial damage[1]. Elevated levels of Tn can be detected within 3-12 h after the start of ischemia and they reach a peak after 12-48 h[2]. However, as Tn is a structural component of myocardial cells, Tn levels will be elevated in patients with chronic heart conditions such as heart failure as well. Therefore, to distinguish between an acute MI and chronic cardiac disease, elevation of Tn alone is not specific enough. There needs to be a significant change in the level of Tn, *i.e.,* a rise and/or a fall. In spontaneous MI a relative difference of more than 20% is considered a significant change[1]. More specifically, in spontaneous MI any level above the 99th percentile is considered a rise[1]. The cut off levels according to the third universal definition for a typical rise in PCI associated MI (> 5 times 99th percentile) and CABG associated MI (> 10 times 99th percentile) are consensus based and not evidence based[1].

The typical rise and/or fall of Tn is thus crucial for the diagnosis of MI[1]. However, the exact shape of the rise and fall curve is largely unknown. Nevertheless, understanding the shape of the rise and fall curve would allow for better timing of Tn blood sampling in clinical practice and would improve diagnostic criteria per type of MI. The aim of this systematic review was to identify the typical shape of the rise and fall curve of Tn following the different types of MI.

MATERIALS AND METHODS

Literature search

Medline (PubMed) and Embase were searched from 1966 through October 2013 for publications. We used synonyms and abbreviations for "rising", "falling", "changing", "troponin" and "myocardial infarction" as keywords (See supplementary 1 for search strategies). Based on titles and abstracts, all studies evaluating Tn in MI were included. Different types of studies were eligible, for example cross sectional studies of patients with MI, cohort studies including patients with symptoms of cardiac ischemia, randomized controlled trials concerning treatment or diagnosis of MI and case control studies where the cases had MI. We included studies in patients with MI that focused on cardiac Tn, both Tn-I and Tn-T, and that reported at least two different Tn-values with at least one sample above the cut off level. Abstracts from conference proceedings, non-human studies, non-English studies, and studies on animals, children, chronic conditions and cardiomyopathy were excluded.

First, all titles and abstracts were screened for eligibility. Second, screening was extended to full text for all studies that where either marked as relevant or when the eligibility was unclear from screening titles and abstracts. Eligibility was determined using a standardized form containing the above mentioned criteria.

The methodological quality of included studies was assessed by two observers (DvB and ML) and in case of doubt by a third observer (BvZ) using an adjusted QUADAS-tool[3] (see supplementary 2 for quality criteria). The selected items of the QUADAS-tool enabled us to examine potential sources of bias and variation[4]. The defined quality domains were; representativeness of the spectrum (*i.e.,* the representativeness of the patients in the study for clinical practice), acceptable reference standard, acceptable delay between tests, partial verification avoided, relevant clinical information, uninterpretable results reported, and withdrawals explained. We did not calculate summary scores estimating the overall-quality of included studies since it has been shown that their interpretation is problematic and may be misleading[5].

Data extraction took place using a specifically designed data extraction form. The two observers independently extracted raw data from the included studies to obtain information on Tn levels at different time points. Other elements that were extracted included the year of publication, the type of study, the research question, any subgroups, inclusion and exclusion criteria, the setting (*e.g.,* emergency department, in hospital, post-surgery) and sample size. In addition, the proportion of patients with MI, the mean or median age of patients with MI, the proportion of males with MI, any comorbidities and the diagnostic criteria used for MI were obtained. Finally, test characteristics were extracted such as the type of Tn test, the 99th percentile/upper reference limit/cut off level of the Tn test, limit of detection, number of samples per patient and the sample time points in relation to the

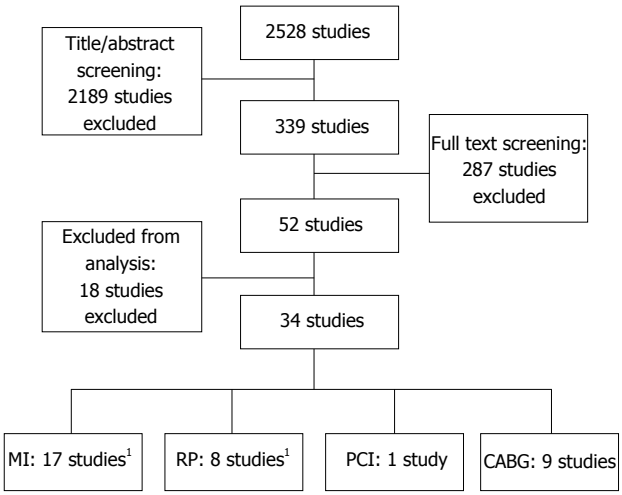

Figure 1 Flow chart. [1]Different data from one study has been included in both the MI and RP analysis. MI: Type 1 spontaneous myocardial infarction; RP: Successful reperfusion during an acute myocardial infarction; PCI: Type 4 myocardial infarction associated with percutaneous coronary intervention; CABG: Type 5 myocardial infarction associated with coronary artery bypass surgery.

event (*e.g.,* admission, surgery).

Data were considered missing if not explicitly mentioned in the text and if impossible to deduct the information directly from other information in the text. Discrepancies between the two observers were resolved by discussion.

Statistical analysis

Studies were divided into four subgroups based on the focus of the articles: Studies on type 1 spontaneous MI, studies that focused on successful reperfusion in the setting of an acute MI (where reperfusion was not initiated or its effect not evaluated), studies on MI associated with PCI (type 4a MI), and studies on MI associated with CABG (type 5 MI). Type 2 MI studies were not included in this systematic review as the etiology behind this type of MI is distinctly different.

In this review we aimed to address the general rise and fall of Tn and not the rise and fall of specific Tn tests. Therefore, all Tn levels that were obtained within 72 h were included in our analysis. If the timing of the samples was not specified, the study was excluded from analysis. If only one data source was available for a given point in time, we excluded this time-point from our analysis.

For each time point up till 72 h we conducted the following procedure. For each study, we first determined the mean and standard deviation (SD) of the Tn values. If available, mean and SD as presented in the article was used. Alternatively, when only a median was available the mean was approximated. For articles with less than 25 patients with MI, we used the formula of Hozo *et al*[6] to approximate the mean, for articles with 25 or more patients with MI, the median was used as the best estimate of the mean. Articles for which the mean could not be approximated were excluded from analysis. When the standard error (SE) was not available from the articles directly, it was calculated from SD, confidence interval (CI), or median absolute deviation. Articles for which the SE was not available nor could be calculated were excluded from the analysis.

Subsequently, in order to make the Tn levels from different studies comparable, all Tn levels were standardized. Standardization was achieved by dividing the Tn levels by the 99th percentile of that particular Tn test. If the 99th percentile was not available, we used the upper reference limit (URL) or the cut off value for standardization. Studies that did not mention a 99th percentile or an URL or a cut off value for their Tn test were excluded from analysis.

After standardization, results over studies were pooled as follows. Every study was assigned a weight according to the inverse of the variance ($1/SE^2$). The weighted mean per article was calculated by multiplying the mean with the weight. The sum of all weighted means was divided by the sum of all weights to calculate a pooled mean for every timepoint. The SE per timepoint was calculated as follows: $1/(\text{sum of the weights})^{0.5}$. From the pooled SE the 95%CI was calculated.

The pooled mean of the standardized Tn levels with the corresponding CI at different time points were analyzed and summarized using a graph.

RESULTS

Search results

Our search resulted in 2528 potentially eligible studies (Figure 1). After screening titles and abstracts 2189 studies were excluded. After reviewing and applying the in- and exclusion criteria to the full text of the remaining 339 studies, 34 studies remained for analysis. There were 17 studies on type 1 spontaneous MI, 8 on successful reperfusion, 1 on MI associated with PCI (type 4), and 9 studies on MI associated with CABG (type 5). One study could be included in the analyses for both type 1 MI and reperfusion. The baseline characteristics of the included studies are summarized in Table 1.

Quality of the included studies

Table 2 describes the results of the quality assessment. Almost all studies avoided partial verification, worked with relevant clinical information and a representative spectrum of patients with MI. Very few studies reported uninterpretable results or explained withdrawals.

Typical rise and fall of Tn

The pooled mean Tn level in type 1 MI showed an early first peak of 7.0 (95%CI: 6.0-8.0) at 1 h. This initial peak was followed by a maximum pooled mean Tn level of 84 (95%CI: 82-86) at 12 h. A third small peak followed at 24 h (2.7; 95%CI: 2.6-2.9) (Figure 2). Finally, there was a gradual fall of Tn.

The maximum pooled mean of Tn after successful reperfusion was at 6 h (1853; 95%CI: 1851-1855), another high peak followed at 24 h (1006; 95%CI: 1004-1007) (Figure 3). Subsequently, there was a pronounced fall in Tn. The pooled mean Tn in type 5 MI associated with CABG raised the first 24 h, after which

Table 1 Baseline characteristics of included studies

Ref.	Year of publication	NO. of patients	Prevalence MI *n* (%)	Males with MI *n* (%)	Diagnostic criteria MI	Tn test	Cut off level	Type of cut off level	Time points measured from
Type 1: Spontaneous MI									
Aldous *et al*[12]	2011	939	200 (21)	NA	Biomarkers ECG Imaging Symptoms	HS-TnT (T) HS-TnI (I)	(T) 0.014 μg/L (I) 0.028 μg/L	(T): 99th (I): 99th	Admission
Aldous *et al*[13]	2012	385	82 (21)	59 (72)	Biomarkers ECG Imaging Symptoms	TnI (I) HS-TnT (T)	(T): 0.014 μg/L (I): 0.028 μg/L	(T): 99th (I): 99th	Admission
al-Harbi *et al*[14]	2002	86	51 (59)	46 (90)	ECG Symptoms	TnI	0.05 ng/mL	99th	Admission
Apple *et al*[15]	2009	381	52 (13)	NA	ESC ACC	TnI	0.034 μg/ L	99th	Admission
Bahrmann *et al*[16]	2013	306	38 (12)	23 (61)	Biomarkers ECG Imaging Symptoms	HS-TnT	14 ng/L	99th	Admission
Bertinchant *et al*[17]	1996	682	48 (7)	41 (85)	WHO	TnI	0.1 μg/L	Cut off	Admission
Biener *et al*[18]	2013	459	111 (3)	82 (74)	WHO UD	HS-TnT	14 ng/mL	99th	Admission
Bjurman *et al*[19]	2013	1504	1178 (75)	716 (61)	Biomarkers ECG Imaging Symptoms	HS-TnT	40 ng/L	99th	Admission
de Winter *et al*[20]	2000	131	131 (100)	NA	Biomarkers Symptoms	TnT	0.1 μg/L	URL	Symptoms
Falahati *et al*[21]	1999	327	62 (19)	NA	WHO	TnT	0.20 μg/L	Cut off	Symptoms
Haaf *et al*[22]	2012	887	127 (14)	87 (69)	Biomarkers ECG Imaging Symptoms	HS-TnT (HT) HS-TnI (HI) TnI (I)	(HT): 0.014 μg/L (HI): 0.009 μg/L (I:) 0.009 μg/L	(HT): 99th (HI): 99th (I:) 99th	Admission
Lucia *et al*[23]	2001	82	42 (51)	32 (76)	Biomarkers ECG Symptoms	TnI	1.5 ng/mL	URL	Admission
Mohler *et al*[24]	1998	100	21 (21)	NA	Biomarkers ECG Symptoms	TnT	0.1 mg/L	Cut off	Admission
Mueller *et al*[25]	2012	863	165 (21)	121 (73)	UD	HS-TnT	14 ng/L	99th	Admission
Reichlin *et al*[26]	2011	836	108 (13)	73 (68)	Biomarkers ECG Imaging Symptoms	Hs-TnT (T) TnI-ultra (I)	(T): 0.014 μg/L (I): 0.04 μg/L	(T): 99th (I): 99th	Admission
Reichlin *et al*[27]	2013	840	120 (14)	81 (68)	Biomarkers ECG Imaging Symptoms	Hs-TnT (T) HS-TnI (I)	(T): 14 ng/L (I): 9 ng/L (I) 9 ng/L	(T): 99th (I): 99th (I): 99th	Admission
Wu[28]	2009	14	4 (29)	4 (100)	NA	TnI-ultra	0.04 μg/L	99th	Admission
Successful reperfusion during acute MI									
Abe *et al*[29]	1994	38	26 (68)	20 (77)	ECG Symptoms	TnT	0.2 ng/mL	URL	Start treatment
Apple et al[30]	1996	25	17 (68)	NA	ECG Symptoms	TnI	3.1 μg/L	URL	Start treatment
Ferraro *et al*[9]	2012	87	87 (100)	68 (78)	NA	TnI-ultra	0.04 μg/L	Cut off	Before and after PCI
Ferraro *et al*[31]	2013	856	360 (42)	253 (70)	Biomarkers ECG Symptoms	TnI-ultra	40 ng/L	99th	Before and after PCI
Mair *et al*[32]	1991	172	33 (18)	NA	WHO	TnT	0.5 μg/L	99th	NA
Ricchiuti *et al*[33]	2000	83	23 (28)	17 (74)	WHO	TnI	0.8 μg/L	URL	End of treatment
Tanasijevic *et al*[34]	1997	30	19 (63)	15 (79)	NA	TnI	0.6 ng/mL	URL	Admission
Tanasijevic *et al*[35]	1999	442	344 (78)	258 (75)	NA	TnI	0.4 ng/mL	Cut off	Before and after treatment
Type 4: MI associated with percutaneous coronary intervention									
Reimers *et al*[36]	1997	80	5 (6)	NA	Biomarkers ECG Imaging	TnT	0.1 μg/L	URL	Before PCI and after
Type 5: MI associated with coronary artery bypass grafting									
Abdel Aziz *et al*[37]	2000	50	14 (28)	14 (100)	Biomarkers	TnT	10 μg/L	Cut off	Declamping

Alyanakian *et al*[38]	1998	41	5 (12)	NA	ECG ECG	TnI	0.6 μg/L	URL	Start CPB
Benoit *et al*[39]	2001	260	8 (3)	NA	Imaging Biomarkers	TnI	0.6 μg/L	URL	Before OR, end of ECC
Fellahi *et al*[40]	1999	102	7 (7)	4 (57)	ECG Imaging ECG	TnI	0.6 ng/mL	Cut off	Admission ICU
Katus *et al*[41]	1991	45	5 (11)	NA	ECG	TnI	0.5 mg/L	URL	After surgery
Lim *et al*[42]	2011	28	9 (32)	7 (78)	UD	TnI-ultra	0.06 μg/L	99th	End of surgery
Mair *et al*[43]	1994	119	10 (8)	9	ECG	TnI (I) TnT (T)	(I): 0.10 μg/L (T): 0.10 μg/L	(I): URL (T): Cut off	Declamping
Thielmann *et al*[44]	2004	55	55 (100)	26 (74)	Biomarkers ECG	TnI	0.5 ng/mL	Cut off	Declamping
Thielmann *et al*[45]	2005	94	94 (100)	67 (71)	Biomarkers ECG	TnI	20 ng/mL	Cut off	Declamping

99th: 99th percentile; ACC: American College of Cardiology; CPB: Cardiopulmonary bypass; ECC: Extracorporeal circulation; ESC: European Society of Cardiology Criteria for MI; HS-TnI: High sensitive TnI; HS-TnT: High sensitive TnT; MI: Myocardial infarction; NA: Not available; PCI: Percutaneous coronary intervention; Tn: Troponin; UD: Universal definition of MI; URL: Upper reference limit; WHO: World Health Organization Criteria for MI.

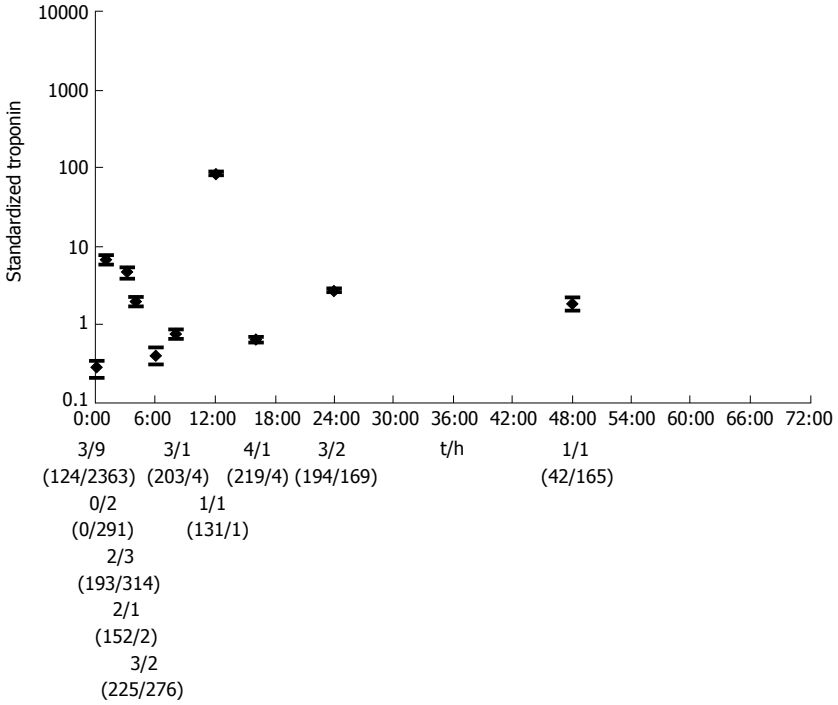

Figure 2 The pooled mean with confidence interval of standardized troponin for the different time points for type 1 spontaneous myocardial infarction. The number of articles per time point with a conventional Tn test/the number of articles with a HS-Tn test, and the number of test values (conventional Tn tests/HS-tests) are shown below the graph. Tn: Troponin; HS: High sensitive.

the Tn levels stabilized (Figure 4). The maximum pooled mean level of Tn was at 72 h (2.2; 95%CI: 1.8-2.6).

DISCUSSION

In this systematic review we identified the typical shape of the rise and fall curve of Tn following type 1 spontaneous MI, after successful reperfusion of a spontaneous MI, and after type 5 MI associated with CABG. The different types of MI resulted in a different peak level of Tn at different time points followed by distinct fall phases. Understanding these variations of Tn kinetics could result in improvement of the specific diagnostic criteria per type of MI.

It is remarkable that for type 5 MI we found the lowest pooled mean peak level of the different types of MI (2.2 compared to 84 in type 1 MI). This is in contrast with what one should expect when applying the third universal definition. In this definition for type 1 MI the recommended cut off level is defined as the 99th percentile and for type 5 MI 10 times the 99th percentile is recommended[1]. First, the relative high levels of Tn that we found for type 1 MI may be the result of the use of high-sensitive Tn tests. Second, the peak level that we have found in our review for type 5 MI is considerably lower than the optimal cut off level for diagnosing type 5 MI according to a previous published study (266 times the URL)[7]. This could be due to the fact that

Table 2 Quality of the included articles based on a modified QUADAS tool

Ref.	1	2	3	4	5	6	7
Type 1: Spontaneous MI							
Aldous *et al*[12]	+	?	-	+	+	?	-
Aldous *et al*[13]	+	+	+	+	+	?	?
al-Harbi *et al*[14]	+	?	+	+	+	?	?
Apple *et al*[15]	+	+	+	+	+	?	?
Bahrmann *et al*[16]	+	+	-	+	-	?	+
Bertinchant *et al*[17]	+	+	+	+	+	?	?
Biener *et al*[18]	+	+	+	+	+	?	?
Bjurman *et al*[19]	+	+	?	+	+	-	?
de Winter *et al*[20]	+	-	+	+	+	?	+
Falahati *et al*[21]	+	+	?	+	+	?	?
Haaf *et al*[22]	+	+	-	+	+	?	+
Lucia *et al*[23]	+	-	?	+	+	?	?
Mohler *et al*[24]	+	+	+	+	+	?	?
Mueller *et al*[25]	+	+	+	+	+	?	?
Reichlin *et al*[26]	+	+	-	+	+	?	?
Reichlin *et al*[27]	+	+	+	+	+	+	+
Wu[28]	+	+	+	+	+	?	?
Successful reperfusion during acute MI							
Abe *et al*[29]	-	+	-	+	-	?	-
Apple *et al*[30]	?	?	-	?	?	?	?
Ferraro *et al*[9]	-	?	+	+	-	-	?
Ferraro *et al*[31]	+	-	?	+	+	?	?
Mair *et al*[32]	+	+	+	+	+	?	-
Ricchiuti *et al*[33]	+	+	+	+	?	?	?
Tanasijevic *et al*[34]	?	?	?	-	?	-	?
Tanasijevic *et al*[35]	-	-	-	?	-	+	?
Type 4: MI associated with percutaneous coronary intervention							
Reimers *et al*[36]	-	+	+	+	?	?	?
Type 5: MI associated with coronary artery bypass grafting							
Abdel Aziz *et al*[37]	+	-	+	+	-	?	?
Alyanakian *et al*[38]	+	+	+	+	-	?	?
Benoit *et al*[39]	+	+	+	+	-	?	?
Fellahi *et al*[40]	+	-	+	+	-	?	+
Katus *et al*[41]	+	-	+	+	-	?	?
Lim *et al*[42]	+	+	+	+	-	+	+
Mair *et al*[43]	-	+	+	+	+	?	?
Thielmann *et al*[44]	+	+	+	+	+	?	?
Thielmann *et al*[45]	+	+	+	+	+	?	?

MI: Myocardial infarction. 1: Representativeness of the spectrum; 2: Acceptable reference standard; 3: Acceptable delay between tests; 4: Partial verification avoided; 5: Relevant clinical; 6: Uninterpretable results reported; 7: Withdrawals explained information.

many of the CABG studies included in our review used a cutoff point instead of a 99th percentile. Likely, these cut off points already take into account the expected higher levels of Tn after CABG. Since we used the cut off level for standardization of Tn if the 99th percentile was not available, this could explain the lower levels of standardized Tn in type 5 MI. In this systematic review we did not include patients without MI from the included studies; therefore we cannot make any claims regarding the optimal diagnostic cut off point.

The recommended interval between two samples to rule MI in or out is 3-6 h[1]. Our results do not support this time interval. For type 1 we found an early first peak after 1 h, followed by a short fall phase. The second rise started at 6 h. This could mean that sampling at 3-6 h might be less optimal than sampling earlier. In type 5 MI the maximum level was at 72 h. Since we did not include any time points after 72 h, we do not know whether this is a peak level or that Tn will rise further. This could mean that Tn should be monitored for more than 72 h postoperatively.

Only one study fulfilled the inclusion criteria focused on type 4 MI. We were therefore unable to analyze the typical rise and fall of Tn after type 4 MI. A review that focused on creatine-kinase M band (CK-MB) in type 4 MI found high levels of CK-MB with a CK-MB level above 10 × URL in 24% of the patients[8].

We found a very large mean peak level of Tn after successful reperfusion in acute MI at 6 h (1853), which is due to one study using a TnI-ultra test in combination with a low cut off level (0.04 μg/L)[9]. It is known that the high sensitive tests require a more pronounced change for the diagnosis MI. While the third universal definition defines a 20% change as significant[1], a rise of > 100% is needed for the high sensitive Tn test[10]. A different cut off level may also be needed for the high-sensitive tests.

This study has several limitations. First, our analysis of the typical rise and fall of Tn is not based on pooling individual patient data from different studies, which would allow for modeling entire biomarker trajectories, but on pooled estimates at different time points used in different studies. To take this into account we refrained from connecting estimates over time. It should however be noted that using individual patient data would be complex as well, given that the studies use a variety of time points; furthermore, the CIs around the pooled estimates are small, so it is rather unlikely that in a substantial number of patients the Tn pattern would be different. Second, we standardized the Tn levels preferentially by using the 99th percentile of Tn. However, the procedure of obtaining a 99th percentile of Tn tests is not uniform[11]. This could result in incorrect standardization and thus restriction of the generalizability. In addition, when the 99th percentile was not available we used the cutoff level. The argumentation for the chosen cutoff level was not always clear. However, the effect of this limitation seems minimal as it may affect the absolute levels of the standardized Tn, but not the Tn rise or fall. Third, the different studies used different criteria to define the baseline time point (0:00 h). These differences were more pronounced in type 1 MI than in type 5 MI articles. This makes the results of type 1 more difficult to interpret. Fourth, we only included studies that focused primarily on Tn levels during MI. This limited the number of included studies. However, the focus of this review was the typical rise and fall of Tn. The excluded studies measured Tn for a different purpose; the timing of the blood sampling and inclusion of the patients was therefore probably not optimal to evaluate the typical rise and fall of Tn. Fourth, Tn levels can be influenced by several patient related factors. For instance, impaired renal function is associated with higher Tn levels. Insufficient patient specific data was available to correct for such patient related factors. However, these factors are likely affecting the absolute levels of Tn and not the

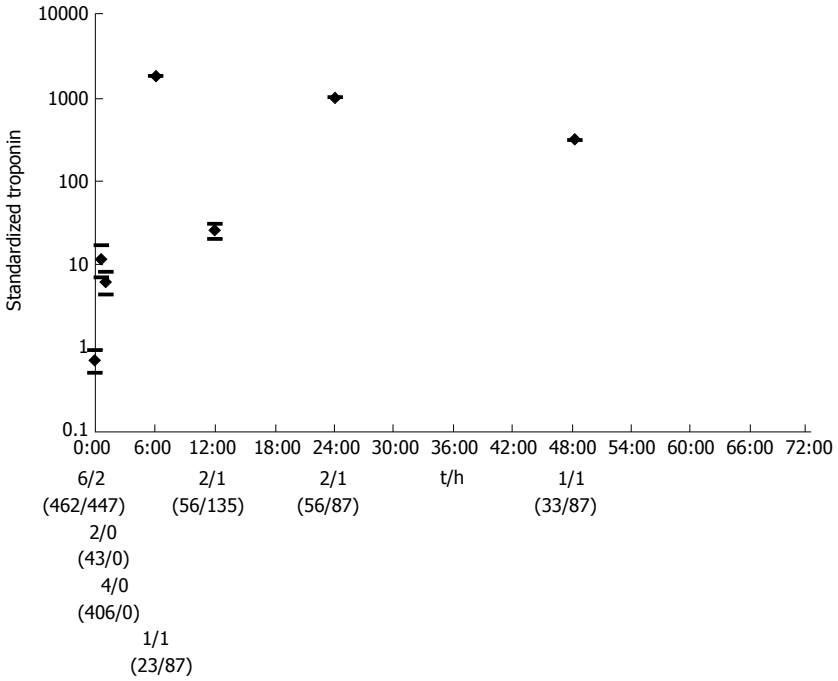

Figure 3 The pooled mean with confidence interval of standardized troponin for the different time points for successful reperfusion after acute myocardial infarction. The number of articles per time point with a conventional Tn test/the number of articles with a HS-Tn test, and the number of test values (conventional Tn tests/HS-tests) are shown below the graph. Tn: Troponin; HS: High sensitive.

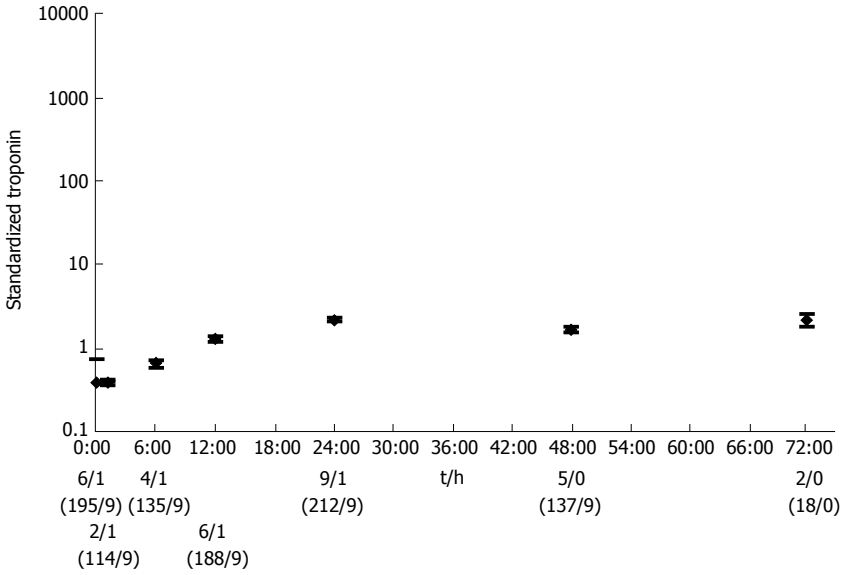

Figure 4 The pooled mean with confidence interval of standardized troponin for type 5 myocardial infarction associated with coronary artery bypass grafting. Time points with only one data source were excluded. The number of articles per time point with a conventional Tn test/the number of articles with a HS-Tn test, and the number of test values (conventional Tn tests/HS-tests) are shown below the graph. Tn: Troponin; HS: High sensitive.

shape of the rise-and-fall curve. Finally, we did not scan the reference lists or related studies identified by Medline from the retrieved studies, nor did we hand-search topic specific journals or conference proceedings. However, our study was not a systematic review focusing on diagnostic accuracy or a therapeutic effect, but merely on the kinetics of Tn. Since only studies that focused on the kinetics of Tn were included we considered that the risk of publication bias was low.

The results of this systematic review give insight in the typical rise and fall of Tn in different types of MI. This systematic review is a first step in understanding the similarities and differences in the Tn kinetics between the different types of MI. The different types of MI each seem to result in a unique rise and fall pattern of Tn. In the future this may allow for optimization of the diagnostic criteria per type of MI. Potentially, understanding the kinetics of Tn can also help in monitoring treatment effec-

tiveness.

COMMENTS

Background

An important diagnostic tool for diagnosing myocardial infarction (MI) is monitoring for dynamic cardiac troponin (Tn) levels. Tn levels are expected to rise and fall in MI. However, the exact shape of the Tn curve in MI is unknown. It is also unknown whether the shape of this curve differs for different types of MI. The aim of this systematic review was to identify the typical shape of the rise and fall curve of Tn following the different types of MI.

Research frontiers

The use of Tn in diagnosing the different types of MI was described by Thygesen *et al* in 2012. For every type of of MI a cut off level and/or the minimum required change in Tn level is suggested for the diagnoses of that particular MI.

Innovations and breakthroughs

An extensive systematic search was conducted to identify all articles concerning the kinetics of Tn in MI type 1, type 4 and type 5. Articles were screened for eligibility and data was extracted in a standardized matter independently by two of the authors. The Tn levels were standardized using the 99th percentile and a pooled mean with 95%CI was calculated for analysis of the results.

Applications

This review suggests that there are important differences in the kinetics of Tn in the different types of MI. Understanding these differences is important for optimizing the diagnostic criteria for these unique types of MI.

Terminology

Myocardial ischemia resulting in myocardial necrosis is called MI. In addition to type 1 spontaneous MI related to atherosclerotic plaque rupture, type 4 MI related to percutaneous coronary intervention and type 5 MI related to coronary artery bypass grafting are classified as distinct types of MI. Cardiac Tn is a sensitive and specific biomarker for myocardial ischemia.

Peer-review

In this systematic review, the authors presented an overview of the typical rise and fall of Tn stratified for the different types of MI.

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