International Journal of Cardiology 228 (2017) 114–121

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Abnormal heart-rate response during cardiopulmonary exercise testing identifies cardiac dysfunction in symptomatic patients with non-obstructive coronary artery disease

Sundeep Chaudhry [a,*], Naresh Kumar [b], Hushyar Behbahani [b], Akshay Bagai [c], Binoy K. Singh [d], Nick Menasco [a], Gregory D. Lewis [e], Laurence Sperling [f], Jonathan Myers [g]

[a] Research and Development, MET-TEST, Inc., Atlanta, GA, United States
[b] Research Division, Whitby Cardiovascular Institute, Whitby, Canada
[c] Division of Cardiology, St. Michael's Hospital, University of Toronto, Canada
[d] Division of Cardiovascular Medicine, Hofstra Northwell School of Medicine, Hofstra University, New York, NY, United States
[e] Cardiology Division, Department of Medicine, Massachusetts General Hospital, Boston, MA, United States
[f] Division of Preventive Cardiology, Emory University, Atlanta, GA, United States
[g] Division of Cardiovascular Medicine, Stanford University and Veterans Affairs, Palo Alto Health Care System, Palo Alto, CA, United States

ARTICLE INFO

Article history:
Received 20 May 2016
Received in revised form 7 November 2016
Accepted 10 November 2016
Available online 14 November 2016

Keywords:
Angina
Ischemic heart disease
Exercise testing
Women

ABSTRACT

Background: Symptomatic non-obstructive coronary artery disease is a growing clinical dilemma for which contemporary testing is proving to be of limited clinical utility. New methods are needed to identify cardiac dysfunction.

Methods and results: This is a prospective observational cohort study conducted from December 2013 to August 2015 in two outpatient cardiology clinics (symptomatic cohort) and 24 outpatient practices throughout the US (healthy cohort) with centralized methodology and monitoring to compare heart-rate responses during cardiopulmonary exercise testing (CPET). Participants were 208 consecutive patients (median age, 61; range, 32–86 years) with exercise intolerance and without prior heart or lung disease in whom coronary anatomy was defined and 116 healthy subjects (median age, 45; range, 26–66 years). Compared to stress ECG, the novel change in heart-rate as a function of work-rate parameter (ΔHR-WR Slope) demonstrated significantly higher sensitivity to detect under-treated atherosclerosis with similar specificity. In men, area under the ROC curve increased from 60% to 94% for non-obstructive CAD and from 64% to 80% for obstructive CAD. In women, AUC increased from 64% to 85% for non-obstructive CAD and from 66% to 90% for obstructive CAD. ΔHR-WR Slope correctly reclassified abnormal studies in the non-obstructive CAD group from 22% to 81%; in the obstructive CAD group from 18% to 84% and in the revascularization group from 35% to 78%.

Conclusion: Abnormal heart-rate response during CPET is more effective than stress ECG for identifying under-treated atherosclerosis and may be of utility to identify cardiac dysfunction in symptomatic patients with normal routine cardiac testing.

1. Introduction

Ischemic heart disease (IHD) caused by coronary atherosclerosis involves multifactorial pathophysiological processes that alter the coronary vasculature and result in endothelial dysfunction, increased microvascular resistance and to varying degrees of obstructive coronary artery disease (O-CAD) [1]. Symptoms (angina) caused by non-obstructive coronary artery disease (NO-CAD) are frequently atypical in nature (dyspnea, fatigue, nausea, and epigastric discomfort), challenging to discern as being cardiac in origin and occur more frequently in women than men [2]. Outcomes data has shown that symptomatic patients with NO-CAD have similar morbidity and mortality as patients with O-CAD [3–7]. Despite a lack of significant coronary obstruction, these patients often have persistent symptoms, recurrent hospitalizations, decreased functional status, increased adverse CV events and consume health care services with repeat medical assessments and procedures [4,8–10]. Recent data has shown that patients with angina and without O-CAD frequently have microvascular ischemia confirmed by functional coronary angiogram studies [11]. The contemporary stress imaging modalities (stress echocardiography and nuclear myocardial perfusion imaging) that were developed to increase sensitivity to detect O-CAD compared to stress ECG are of limited value in detecting inducible microvascular ischemia

* Corresponding author at: MET-TEST, Inc., 1117 Perimeter Center West, Suite W-211, Atlanta, GA 30338, United States.
E-mail address: schaudhry@mettest.net (S. Chaudhry).

http://dx.doi.org/10.1016/j.ijcard.2016.11.235

in symptomatic patients with NO-CAD [12–15]. As a result, stress ECG is still the recommended initial procedure for non-invasive evaluation of women at intermediate risk for suspected IHD [16].

Accurate detection of inducible ischemia from NO-CAD is a growing clinical dilemma for which current clinical tools are not adequate and new methodologies need to be developed. The ability for cardiopulmonary exercise testing (CPET) to detect left-ventricular dysfunction caused by inducible ischemia is recognized as a new application by the American Heart Association [17]. CPET provides a physiologic quantification of the WR, HR, and oxygen uptake (VO_2) at which myocardial dysfunction develops [18]. The depletion of high energy phosphate bonds past the ischemic threshold results in mechanical dysfunction during exercise with subsequent decrease in stroke volume with increasing work-rate. Since cardiac output to the working skeletal muscles must increase with progressively increasing resistance, the autonomic nervous system response is up-regulated at the ischemic threshold and the HR response is accelerated from baseline as a compensatory mechanism to meet the body's increasing need for peripheral perfusion. The ischemia may be diffuse and evenly distributed or regional, from small or large vessel disease; the significance of a heightened HR response is that a global cardiac problem exists. Mechanical dysfunction may subsequently be followed by ECG changes and symptoms comprising the ischemic cascade [19]. In this regard, careful analysis of oxygen uptake kinetics has been shown to be superior to traditional stress ECG for the diagnosis of O-CAD in two studies assessing patients with chest pain [20,21]. Greater clarity is needed to define the role of CPET in the evaluation of IHD. The purpose of this study is to quantitate differences in HR response patterns in a cohort of healthy subjects with a cohort of symptomatic patients assessed by CPET using coronary angiogram as the gold standard to quantify the degree of large vessel atherosclerosis in a real-world clinical setting.

2. Methods

2.1. Patient selection

The symptomatic cohort comprised of 208 consecutive symptomatic patients referred by their primary care physicians to two outpatient cardiology practices (Toronto and New York) for evaluation of exercise intolerance (chest pain and shortness of breath) between December 1, 2013 and August 31, 2015. Exclusion criteria included a prior history of heart or lung disease. Exclusion criteria after CPET included: 1) insufficient effort (peak respiratory exchange ratio (RER) ≤ 1.05, unless there was a plateau in O_2-pulse after the ventilatory anaerobic threshold (VAT) as an indicator of LV dysfunction) and 2) systolic blood pressure at peak exercise >220 mm Hg. All patients with a plateau in the O_2-pulse (VO_2/HR) or with visual evidence of acceleration of HR response as a function of work-rate or VO_2 were considered abnormal and referred for invasive coronary angiogram [18]. Symptomatic patients with normal CPET responses were referred for coronary CT angiogram to assess coronary anatomy. Informed consent was obtained from all subjects prior to each study.

A healthy cohort was developed to establish a normal HR response pattern. The MET-TEST database ($n = 136.392$) was queried for asymptomatic individuals with no CV risk factors, BMI < 30, and not on any cardiovascular medications. The normal cohort was tested during the same time as the recruitment period of symptomatic patients with the same protocol and were selected from 24 centers throughout the US. The reason for testing was annual physical fitness evaluation and/or peak aerobic performance evaluation (commercial pilots, fire-fighters, military, police and recreational athletes). Subjects had to put forth good effort (peak RER ≥ 1.05) with normal peak VO_2 (85–130% of predicted), normal peak HR (85–110% of age predicted maximum) and without ECG changes (no ST depression or arrhythmias) to be included for HR analysis. A total of 116 subjects qualified for inclusion with a near equal number of men and women.

2.2. Cardiopulmonary exercise testing (CPET)

Symptom-limited CPET was performed on an electromagnetically-braked cycle ergometer using a customized linear-ramp protocol designed to elicit fatigue within 8 to 12 min of exercise. Details of the protocol and equipment have been described earlier [18]. The ventilatory anaerobic threshold (VAT) was determined using the V-slope method [22]. Breath-by-breath measured parameters and predicted equations were collected and interpreted as described by Wasserman et al.. [23]. Numerical results were reported as a 10 second average and graphical results were displayed using a 20 second average. Medications were not withheld in the symptomatic cohort prior to testing as the purpose of the CPET was to determine the mechanism of exercise impairment. All systems were owned and operated by MET-TEST with centralized calibration and equipment performance monitoring from the data center. All technicians were trained and monitored by MET-TEST and each technician acted as a biological control for their system. Data from all sites was analyzed and maintained in a central database.

Subjects without atherosclerotic heart disease and normal LV function tend to maintain a linear HR response throughout exercise when a linear work load is imposed. Fig. 1A depicts a normal response in a healthy subject. Subjects with physiologically significant ischemic burdens will develop mechanical dysfunction at some point after the VAT and before the end of exercise when myocardial oxygen demand exceeds supply. The HR response steepens from baseline at the start of mechanical dysfunction due to increased sympathetic discharge under the control of the autonomic nervous system. Fig. 1B depicts a pathological response in a patient with three-vessel O-CAD who underwent coronary artery bypass graft surgery in this study.

A new mathematical model was developed to objectively quantify the compensatory HR response after the onset of mechanical dysfunction. The first few minutes of low intensity exercise represent the warm up period and there is a delay in the rise in HR [23]. The HR will start to increase after the warm-up period and establishes a reliable baseline in the two-minute period before the VAT. The line of best fit was calculated using the least squares method at two places during exertion. Slope one (S1) represents the slope of the line of best fit of the 10 second averaged data points over the course of the 2 min before the VAT. Slope two (S2) represents the slope of the line of best fit of the 10 second averaged data points for the last 2 min of exercise prior to test termination. The change in slope is calculated as percent change from baseline and equals the difference in S2 and S1 divided by S1 and multiplied by 100. This calculation is expressed as the ΔHR-WR Slope parameter and represents the change in HR slope in late exercise as a function of increasing work-rate (Watts).

Stress ECG was analyzed for ST changes at peak exercise. A normal response was defined as a lack of significant ST-segment changes. A positive response was defined as ST-segment depression of 1 mm or greater (upsloping or flat) in ≥2 leads. Studies were considered indeterminate if they had significant artifact or other abnormalities such as left bundle branch block or ST-segment change <1 mm. All studies were interpreted by one investigator not situated with any site.

2.3. Coronary angiograms

Coronary angiograms were performed in two tertiary care centers as part of routine clinical care within 30 days of CPET. One cardiologist from each center was responsible for recording all angiogram results into the database and was blinded to the CPET results. Coronary angiogram results were categorized as "normal" if the epicardial arteries were completely free of disease; "NO-CAD" if there were one or more arteries with one or more lesions that resulted in up to 50% stenosis; and as "O-CAD" if lesions were >50% stenotic. Each category represents a progressively higher global atherosclerotic disease burden for which diagnostic and outcomes data were available from prior publications with similar categorizations.

2.4. Statistical analysis

Values are depicted as their mean ± SE or *n* (%). Gender differences in age and body mass index were analyzed using the Student's *t*-test. Chi-square tests were used to compare gender differences between risk factors. Differences between the healthy and symptomatic cohorts for key peak exercise parameters were analyzed using a one-way ANOVA and statistically significant differences were subject to post-hoc analysis using the Bonferroni post-hoc test. The receiver operator characteristic (ROC) curve was used to identify the optimal cut-off point for ΔHR-WR Slope to identify cardiac dysfunction in patients with documented NO-CAD, O-CAD and revascularization. The optimal values for sensitivity and specificity were determined by choosing the threshold closest to the upper left corner of the ROC curve. These values were compared to the diagnostic accuracy of stress ECG. A confidence interval of 95% was used and p values < 0.05 were considered statistically significant. Data was analyzed using SPSS© version 22. ROC analysis was performed using the life science module of XLSTAT version 2015.4.01.20116 (www.xlstat.com).

3. Results

All studies (CPET, CT angiograms and invasive coronary angiograms) were performed without complications. Baseline characteristics of the study population are shown in Table 1. The distribution of coronary angiogram results is shown in Fig. 2. The prevalence of NO-CAD and O-CAD in the symptomatic cohort was 32% and 50% respectively with 26% of the patients undergoing revascularization. Men had the lowest incidence of normal coronaries and the highest incidence of O-CAD while women had near equal distribution of normal coronaries, NO-CAD and O-CAD. Women were ~3 times more likely to have normal coronaries compared to men and men were ~2 times more likely to undergo revascularization compared to women in this study.

The key peak exercise parameters for men and women are listed in Table 2. While men demonstrated an incremental linear decline in mean peak VO_2 and peak O_2-pulse values with progression of atherosclerotic-burden, symptomatic women with normal coronaries

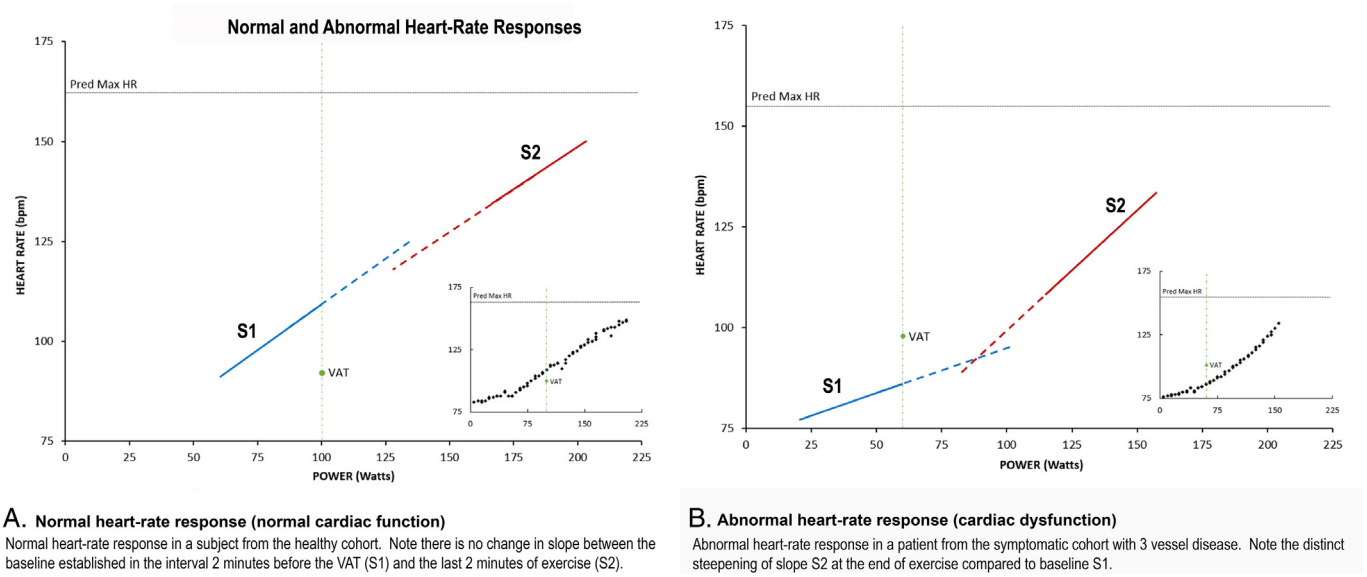

Fig. 1. Normal and abnormal heart-rate responses. S1 = slope of line of best fit for heart-rate response in 2 min prior to the ventilatory anaerobic threshold. S2 = slope of line of best fit for heart-rate response in 2 min prior to end of exercise. VAT = Ventilatory Anaerobic Threshold.

had a significant decrease in both parameters as well with less progression observed in the NO-CAD, O-CAD and revascularization groups (Fig. 3). The mean ΔHR-WR Slope values in each category are shown in Fig. 4. This parameter has a slight negative value in the healthy cohort and progressively increases with increasing atherosclerotic burden in both men and women. Post-hoc analysis for men revealed that the mean value of the healthy cohort was significantly different from the symptomatic normal coronary ($p = 0.006$), NO-CAD ($p < 0.001$), O-CAD ($p < 0.001$) and revascularization groups ($p < 0.001$). Post-hoc analysis for women revealed that the mean value of the healthy cohort was not significantly different from the symptomatic normal coronary group ($p = 1.0$) but was for the NO-CAD ($p = 0.001$), O-CAD ($p < 0.001$) and revascularization groups ($p < 0.001$).

ROC Curve Analysis results comparing ΔHR-WR Slope with stress ECG are listed in Table 3. The listed ΔHR-WR Slope cutoff values represent the highest area under the ROC curve. Compared to stress ECG in both men and women, ΔHR-WR Slope demonstrates significantly higher sensitivity with little loss in specificity for detection of atherosclerotic burden in the NO-CAD, O-CAD and revascularization groups in the symptomatic cohort. PPV was slightly better for stress ECG and NPV was slightly better for ΔHR-WR Slope. As a result of increased sensitivity, the percentage of studies that were reclassified as abnormal with ΔHR-WR Slope analysis compared to stress ECG increased from 10% to 55% in the symptomatic normal coronary artery category. Based on coronary angiogram results, the percentage of studies correctly reclassified as abnormal compared to stress ECG increased from 22% to 81% in the NO-CAD category, from 18% to 84% in the O-CAD category and from 35% to 78% in the revascularization category.

Table 1
Patient characteristics.

	Healthy cohort		Symptomatic cohort		
	Men ($n = 57$)	Women ($n = 59$)	Men ($n = 134$)	Women ($n = 74$)	p Value
Age (yrs)	43 ± 1	47 ± 1	60 ± 1	59 ± 1	0.51
BMI (kg/m^2)	28.4 ± 0.4	27.2 ± 0.7	28.5 ± 0.4	28.4 ± 0.9	0.89
Smoker	n/a	n/a	23	12	0.86
Diabetes	n/a	n/a	43	9	<0.05
Hypertension	n/a	n/a	74	33	0.14
Dyslipidemia	n/a	n/a	91	45	0.30
Family history	n/a	n/a	68	46	0.11
Statin	n/a	n/a	73	33	0.17
Beta-blocker	n/a	n/a	28	14	0.73
CCB	n/a	n/a	8	3	0.55
ACEI	n/a	n/a	31	14	0.48
ARB	n/a	n/a	24	9	0.28
ASA	n/a	n/a	63	31	0.48
Nitrates	n/a	n/a	4	4	0.39
Diuretic	n/a	n/a	10	6	0.87

Values are mean ± SE. p Values compare males and females in the symptomatic cohort. Gender differences in age & BMI were analyzed using an independent t-test. Gender differences in risk factors were analyzed using the chi square test. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ASA = aspirin; CCB = calcium channel blocker.

4. Discussion

The current analysis represents the first report comparing a normal HR response in a cohort of healthy individuals with a pathological HR response in a cohort of symptomatic individuals with different degrees of coronary atherosclerotic burden. Because the HR response is under the control of the autonomic nervous system and is affected by cardiac pathology, it serves as a superior parameter to determine whether the cause of a patient's symptoms is cardiac in origin or not. This compensatory mechanism provides proof that the net effect of atherosclerotic heart disease has become physiologically significant and is impairing cardiac function during exertion resulting in symptoms. Atherosclerosis has multiple effects on cardiac structure and function and affects men and women in different ways. It is possible to have inducible ischemia independent of large vessel flow limitation caused by obstructive coronary artery disease. Mechanisms for IHD include endothelial dysfunction, decreased coronary flow reserve (CFR) from increased microcirculatory resistance (arteriolar wall remodeling with or without micro-thrombi) and microvascular spasms [1,11,24–27]. All of these mechanisms have been shown to increase CV events and worsen prognosis in patients without O-CAD [28–31]. The initial clinical evaluation of patients without a prior history of heart disease can be greatly enhanced if a parameter can accurately identify the net effect of these mechanisms and guide further evaluation. The novel ΔHR-WR Slope parameter presented in the current study has the potential to fill this role and significantly outperformed stress ECG in this capacity, which is still the current recommendation for the initial non-invasive evaluation of women at intermediate risk for suspected IHD [16]. Calculation of ΔHR-WR Slope can be performed by other methods. The process requires a strictly linear work

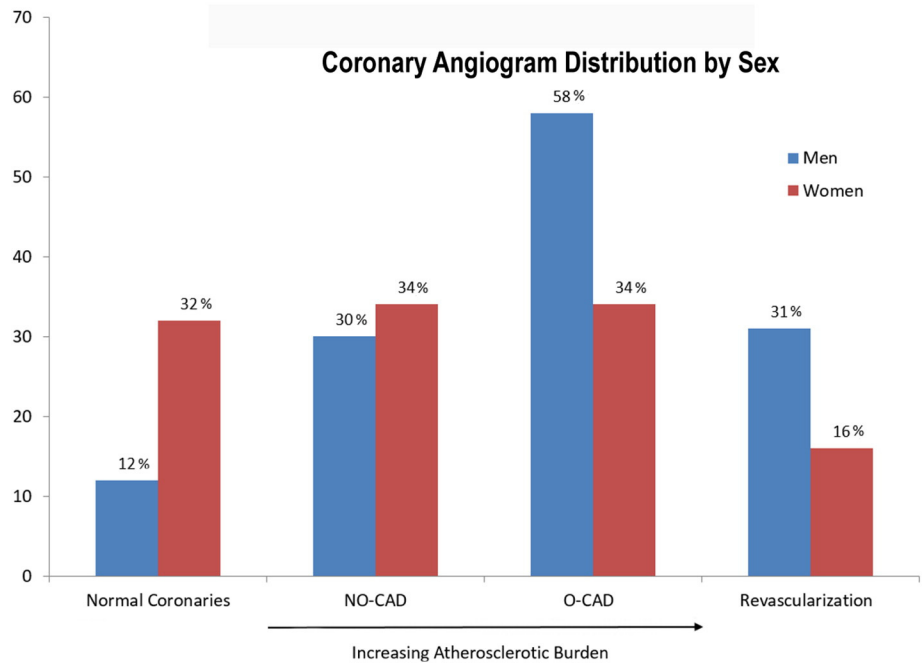

Fig. 2. Coronary angiogram distribution by sex. NO-CAD = Non-obstructive coronary artery disease (≤50%). O-CAD = Obstructive coronary artery disease (>50%).

ramp with minimal motion artifact and a reference point mid-exercise to establish a baseline HR slope to compare the HR slope at the end of exercise. CPET has the advantage of using the VAT as a reliable mid-exercise reference point. The VAT varies in individuals and the calculation requires measurement of both oxygen consumption and carbon dioxide production during exercise.

4.1. Diagnosis (ΔHR-WR Slope)

To put exercise diagnostic parameters into perspective, the WOMEN trial documented a 20% stress ECG abnormality rate and a 9% nuclear myocardial perfusion imaging abnormality rate in women similar to this study. ΔHR-WR Slope approximately quadrupled the number of abnormal studies compared to stress ECG in women with NO-CAD. This means that ΔHR-WR Slope would increase the number of abnormal studies approximately 8 fold compared to nuclear myocardial perfusion imaging (MPI). Recent data has shown that microvascular dysfunction in symptomatic patients with NO-CAD is nearly equally prevalent in men and women (60% and 66% respectively) and correlates poorly with conventional CV risk factors [11]. Our results reveal that in men, ΔHR-WR Slope in the revascularization and O-CAD groups is significantly different from the healthy cohort ($p < 0.001$) and not statistically different compared to the NO-CAD and symptomatic normal coronary groups ($p = 0.88$ and 0.65 respectively) with 60% of men with NO-CAD having been demonstrated to have microvascular dysfunction. Likewise, in women, ΔHR-WR Slope in the revascularization and O-CAD groups is highly statistically different from the healthy cohort ($p < 0.001$) and not statistically different compared to the NO-CAD and symptomatic normal coronary groups ($p = 0.55$ and 0.057 respectively) with 66% of women with NO-CAD demonstrated to have microvascular dysfunction. This data indicates that there is little physiological difference between NO-CAD and O-CAD in symptomatic patients with

Table 2
Key peak exercise parameters.

Men						
	Healthy cohort ($n = 57$)	Symptomatic cohort ($n = 177$)				p Value
		Normal coronaries ($n = 16$)	NO-CAD ($n = 40$)	O-CAD ($n = 78$)	Revascularization ($n = 43$)	
Mean peak VO_2	96.7 ± 0.8%	86.4 ± 5.6%	76.6 ± 2.1%	70.5 ± 1.6%	68.4 ± 2%	<0.05
Mean peak O_2-pulse	106 ± 1.2%	94 ± 5.6%	88.4 ± 2.5%	85.5 ± 1.9%	84.1 ± 2.7%	<0.05
Mean ΔHR-WR Slope	−4.6% ± 4%	+88 ± 33%	+105 ± 13%	+102 ± 13%	+84 ± 17%	<0.05
ST changes	0 (0%)	0 (0%)	8 (20%)	21 (27%)	14 (33%)	<0.05
Women						
	Healthy cohort ($n = 59$)	Symptomatic cohort ($n = 86$)				p Value
		Normal coronaries ($n = 24$)	NO-CAD ($n = 25$)	O-CAD ($n = 25$)	Revascularization ($n = 12$)	
Mean peak VO_2	98.4 ± 1%	86.7 ± 3.9%	85.7 ± 2.5%	86.6 ± 2.3%	85.3 ± 2.2%	<0.05
Mean peak O_2-pulse	106.6 ± 1.2%	97.1 ± 3.5%	100.8 ± 4%	99.4 ± 2.6%	101.2 ± 2.6%	<0.05
Mean ΔHR-WR Slope	−7% ± 5.5%	+36 ± 25%	+105 ± 28%	+130 ± 30%	+153 ± 58%	<0.05
ST changes	0 (0%)	4 (17%)	7 (28%)	8 (32%)	5 (42%)	<0.05

Values are mean ± SE or n (%). Symptomatic men and women have significantly lower peak VO_2 and acceleration of HR response in late phase exercise (ΔHR-WR Slope) compared to healthy cohorts.
ΔHR-WR Slope = change in heart-rate as a function of work-rate slope in the last 2 min of exercise from baseline. The p value compares statistical significance between the means in each row using a one-way ANOVA.

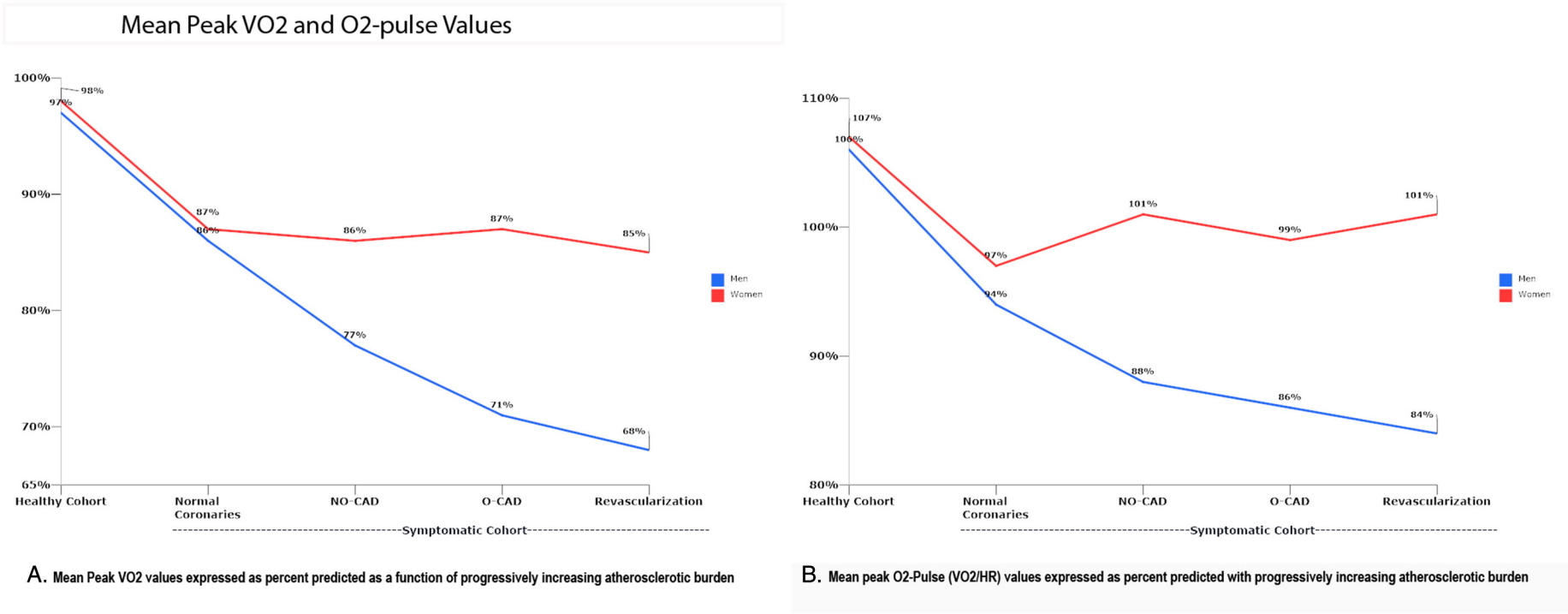

Fig. 3. Mean peak VO_2 (A) and peak (B) O_2-pulse values by coronary angiogram class. NO-CAD = Non-obstructive coronary artery disease (≤50%). O-CAD = Obstructive coronary artery disease (>50%).

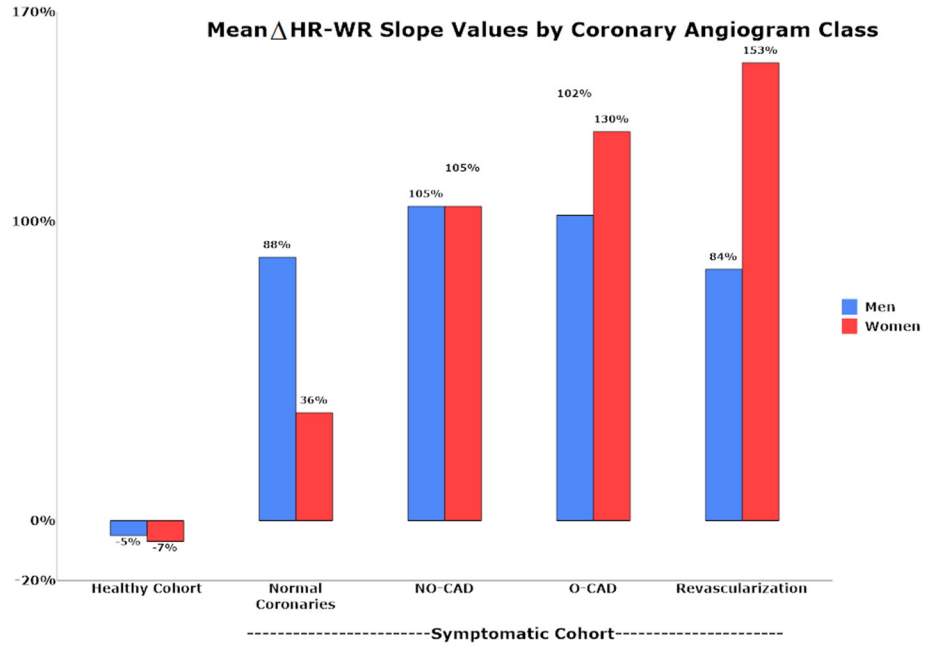

Fig. 4. Mean ΔHR-WR Slope values by coronary angiogram class. ΔHR-WR Slope = Change in heart-rate as a function of work-rate slope in the last 2 min of exercise from baseline = (S2 − S1 ÷ S1) × 100. NO-CAD = Non-obstructive coronary artery disease (≤50%). O-CAD = Obstructive coronary artery disease (>50%).

differing degrees of large vessel atherosclerotic burden. Both categories have cardiac dysfunction based on abnormal ΔHR-WR Slope that is driving symptoms and clinical events. Whether inducible ischemia is a common denominator in patients with O-CAD and NO-CAD with cardiac dysfunction on CPET requires further investigation. Symptomatic patients with cardiac dysfunction and NO-CAD are still in need of a definitive diagnosis. The next step would be to assess coronary endothelial function and measure coronary flow reserve. These assessments can be performed invasively during coronary angiogram with acetylcholine and adenosine challenges [25]. Non-invasive measurement of coronary flow reserve can be performed by ultrasound techniques [13,30], cardiac positron emission tomography (Cardiac PET) [32] and cardiac MRI [33].

Non-atherosclerotic causes of cardiac dysfunction should also be considered. Other mechanisms that can cause myocardial energy depletion during exertion include congenital disorders (hypertrophic cardiomyopathy, anomalous coronary anatomy, myocardial bridging, and mitochondrial cardiomyopathy), valve disease (severe aortic stenosis and mitral regurgitation) and hypertensive systolic blood pressure response (SBP ≥ 220 mm Hg).

Table 3
ROC analysis comparing ΔHR-WR Slope with stress ECG.

Men						
	NO-CAD (n = 40)		O-CAD (n = 78)		Revascularization (n = 43)	
	Stress ECG	ΔHR-WR Slope Cutoff = 17%	Stress ECG	ΔHR-WR Slope cutoff =14%	Stress ECG	ΔHR-WR Slope cutoff = 14%
AUC	60%	94%	64%	80%	66%	83%
Sensitivity	20% (95% CI, 10–35%)	95% (95% CI, 82–99%)	27% (95% CI, 18–38%)	86% (95% CI, 76–92%)	33% (95% CI, 21–48%)	79% (95% CI, 65–89%)
Specificity	100% (95% CI, 92–100%)	79% (95% CI, 67–88%)	100% (95% CI, 92–100%)	79% (95% CI, 67–88%)	100% (95% CI, 92–100%)	79% (95% CI, 67–88%)
PPV	100%	76%	100%	85%	100%	74%
NPV	64%	96%	50%	80%	66%	83%
Accuracy	67%	86%	58%	83%	71%	79%
Women						
	NO-CAD (n = 25)		O-CAD (n = 25)		Revascularization (n = 12)	
	Stress ECG	ΔHR-WR Slope cutoff = 68%	Stress ECG	ΔHR-WR Slope cutoff = 70%	Stress ECG	ΔHR-WR Slope cutoff = 81%
AUC	64%	85%	66%	90%	71%	89%
Sensitivity	28% (95% CI, 14–48%)	68% (95% CI, 48–83%)	32% (95% CI, 17–52%)	76% (95% CI, 56–89%)	42% (95% CI, 19–68%)	75% (95% CI, 46–92%)
Specificity	100% (95% CI, 92–100%)	95% (95% CI, 85–99%)	100% (95% CI, 93–100%)	97% (95% CI, 88–100%)	100% (95% CI, 93–100%)	98% (95% CI, 90–100%)
PPV	100%	85%	100%	90%	100%	90%
NPV	77%	88%	78%	90%	89%	95%
Accuracy	79%	87%	80%	90%	90%	94%

ΔHR-WR Slope demonstrates significantly higher sensitivity for detection of under-treated atherosclerotic burden compared to stress ECG with similar specificity resulting in improved diagnostic accuracy. PPV is higher for stress ECG and NPV is higher for ΔHR-WR Slope.
ΔHR-WR Slope = change in heart-rate as a function of work-rate slope in the last 2 min of exercise from baseline.
NO-CAD = non-obstructive coronary artery disease (≤50%).
O-CAD = obstructive coronary artery disease (>50%).
AUC = area under receiver operating curve (ROC).
PPV = positive predictive value. NPV = negative predictive value.

4.2. Prognosis (peak VO_2)

Aside from providing diagnostic value by assessing for cardiac dysfunction, CPET is the gold standard for quantifying cardiorespiratory fitness (CRF) for prognostic purposes because it directly measures peak VO_2 as opposed to estimating exercise capacity. Of all exercise and imaging based parameters, CRF (peak VO_2) has proven to be the #1 predictor of all-cause mortality in men and women without known CAD as well as mortality in patients with known CAD [34–37]. Direct measurement of peak VO_2 enables more precise risk stratification at baseline as well as the ability to track changes in clinical status with serial testing. The male patients in this study exhibited a linear incremental decline in peak VO_2 with increasing atherosclerotic burden indicating progressively worsening prognosis with the lowest mean peak $VO_2 = 68\%$ of age-predicted in the revascularization group. Symptomatic women reveal a clear decline compared to the healthy cohort but little change with progression of atherosclerotic burden with relatively well preserved functional capacity of 85% of age-predicted in the revascularization group. This may be a reflection of the lesser degree of large vessel atherosclerosis seen in women compared to men. The finding of preserved functional capacity in symptomatic women with suspected ischemic heart disease is consistent with prior reports [38]. The goal of any type of therapeutic intervention in patients with IHD is to improve quality of life and survival and direct measurement of peak VO_2 after cardiac rehabilitation predicts long-term prognosis [39]. Exercise has a protective effect independent of traditional risk factors [40]. Quantifying Peak VO_2 assesses all beneficial aspects as well as monitoring compliance. Because exercise and medical therapy are the cornerstones of treatment for patients with NO-CAD, serial peak VO_2 comparison enables a higher degree of precision for clinical tracking on an individual basis.

4.3. Limitations

This study is a comparison between a younger asymptomatic, presumed healthy cohort and a relatively older symptomatic cohort. By its very nature, the presence of heart disease is going to lower peak VO_2 and thus result in a difference in fitness levels between the two groups. Having age and sex matched asymptomatic, relatively sedentary individuals without cardiovascular risk factors would have made for a more ideal healthy cohort but was not feasible in this clinical observational study. It was also assumed that all patients in the healthy cohort had no IHD and the presence of subclinical IHD may explain increased ΔHR-WR Slope values in some subjects. Heart-rate limiting medications were not withheld prior to CPET. Blunting of HR response will skew each study towards a normal response. Men had a higher rate of diabetes than women in our population and this may be a contributing factor for the higher degree of large vessel atherosclerosis and lower observed peak VO_2. As with most diagnostic studies, the presence of work-up bias must be considered since many subjects had diagnostic procedures as a result of their exercise test results. Since this study required clinical judgement in real-world situations, work-up bias was unavoidable. Fractional flow reserve (FFR) was not measured as this procedure is not routinely performed at the participating hospitals. This study did not track long-term effects on cardiovascular end points or downstream resource utilization. Future studies should correct for these limitations.

4.4. Future research

Because there was no significant difference in the ΔHR-WR Slope parameter between the symptomatic normal coronary, NO-CAD and O-CAD groups in both sexes with symptoms, it is possible that microvascular dysfunction is the common link between the three groups. Individuals with greater large vessel atherosclerosis burden are also likely to have microvascular disease. Future research should assess detailed coronary physiological function in all three groups and peak VO_2 should be closely monitored to correlate with long-term CV events.

5. Conclusion

This study demonstrates that cardiopulmonary exercise testing is more effective than traditional stress ECG for the detection of obstructive and non-obstructive coronary artery disease when used in the initial evaluation of patients suspected of having IHD. The novel ΔHR-WR Slope parameter significantly increased the sensitivity to detect under-treated atherosclerosis verified by coronary angiogram with little loss in specificity. CPET is particularly suited as the first line tool for the assessment of symptoms in women because of low cost, safety (no radiation), superior sensitivity and widespread availability in most hospitals. An abnormal study confirms that common atypical symptoms are cardiac in origin and further evaluation is warranted.

Disclosures

Sundeep Chaudhry and Nick Menasco are employees and hold equity at MET-TEST. Other authors do not have any conflict of interests to report. There was no funding associated with this research project.

Acknowledgements

None.

References

[1] M. Marzilli, C.N. Merz, W.E. Boden, et al., Obstructive coronary atherosclerosis and ischemic heart disease: an elusive link! J. Am. Coll. Cardiol. 60 (11) (2012) 951–956.
[2] C.N. Bairey Merz, L.J. Shaw, S.E. Reis, et al., Insights from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study: part II: gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease, J. Am. Coll. Cardiol. 47 (Suppl. 3) (2006) S21–S29.
[3] L. Jespersen, A. Hvelplund, S.Z. Abildstrom, et al., Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events, Eur. Heart J. 33 (6) (2012) 734–744.
[4] B.D. Johnson, L.J. Shaw, S.D. Buchthal, et al., Prognosis in women with myocardial ischemia in the absence of obstructive coronary disease: results from the National Institutes of Health-National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE), Circulation 109 (24) (2004) 2993–2999.
[5] F.Y. Lin, L.J. Shaw, A.M. Dunning, et al., Mortality risk in symptomatic patients with nonobstructive coronary artery disease: a prospective 2-center study of 2,583 patients undergoing 64-detector row coronary computed tomographic angiography, J. Am. Coll. Cardiol. 58 (5) (2011) 510–519.
[6] T.M. Maddox, M.A. Stanislawski, G.K. Grunwald, et al., Nonobstructive coronary artery disease and risk of myocardial infarction, JAMA 312 (17) (2014) 1754–1763.
[7] R. Rossini, D. Capodanno, C. Lettieri, et al., Long-term outcomes of patients with acute coronary syndrome and nonobstructive coronary artery disease, Am. J. Cardiol. 112 (2) (2013) 150–155.
[8] M.B. Olson, S.F. Kelsey, K. Matthews, et al., Symptoms, myocardial ischaemia and quality of life in women: results from the NHLBI-sponsored WISE study, Eur. Heart J. 24 (16) (2003) 1506–1514.
[9] L.J. Shaw, C.N. Merz, C.J. Pepine, et al., The economic burden of angina in women with suspected ischemic heart disease: results from the National Institutes of Health-National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation, Circulation 114 (9) (2006) 894–904.
[10] R. Tavella, N. Cutri, G. Tucker, R. Adams, J. Spertus, J.F. Beltrame, Natural history of patients with insignificant coronary artery disease, Eur. Heart J. Qual. Care Clin. Outcomes 2 (2) (2016) 117–124.
[11] J.D. Sara, R.J. Widmer, Y. Matsuzawa, R.J. Lennon, L.O. Lerman, A. Lerman, Prevalence of coronary microvascular dysfunction among patients with chest pain and nonobstructive coronary artery disease, JACC Cardiovasc. Interv. 8 (11) (2015) 1445–1453.
[12] A. Cassar, P. Chareonthaitawee, C.S. Rihal, et al., Lack of correlation between noninvasive stress tests and invasive coronary vasomotor dysfunction in patients with nonobstructive coronary artery disease, Circ. Cardiovasc. Interv. 2 (3) (2009) 237–244.
[13] N.D. Mygind, M.M. Michelsen, A. Pena, et al., Coronary microvascular function and cardiovascular risk factors in women with angina pectoris and no obstructive coronary artery disease: the iPOWER study, J. Am. Heart Assoc. 5 (3) (2016).
[14] A. Rozanski, H. Gransar, S.W. Hayes, et al., Temporal trends in the frequency of inducible myocardial ischemia during cardiac stress testing: 1991 to 2009, J. Am. Coll. Cardiol. 61 (10) (2013) 1054–1065.

[15] L.J. Shaw, J.H. Mieres, R.H. Hendel, et al., Comparative effectiveness of exercise electrocardiography with or without myocardial perfusion single photon emission computed tomography in women with suspected coronary artery disease: results from the What is the Optimal Method for Ischemia Evaluation in Women (WOMEN) trial, Circulation 124 (11) (2011) 1239–1249.
[16] J.H. Mieres, M. Gulati, N. Bairey Merz, et al., Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease: a consensus statement from the American Heart Association, Circulation 130 (4) (2014) 350–379.
[17] G.J. Balady, R. Arena, K. Sietsema, et al., Clinician's guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association, Circulation 122 (2) (2010) 191–225.
[18] S. Chaudhry, R. Arena, K. Wasserman, et al., Exercise-induced myocardial ischemia detected by cardiopulmonary exercise testing, Am. J. Cardiol. 103 (5) (2009) 615–619.
[19] M.T. Upton, S.K. Rerych, G.E. Newman, S. Port, F.R. Cobb, R.H. Jones, Detecting abnormalities in left ventricular function during exercise before angina and ST-segment depression, Circulation 62 (2) (1980) 341–349.
[20] R. Belardinelli, F. Lacalaprice, F. Carle, et al., Exercise-induced myocardial ischaemia detected by cardiopulmonary exercise testing, Eur. Heart J. 24 (14) (2003) 1304–1313.
[21] R. Belardinelli, F. Lacalaprice, L. Tiano, A. Mucai, G.P. Perna, Cardiopulmonary exercise testing is more accurate than ECG-stress testing in diagnosing myocardial ischemia in subjects with chest pain, Int. J. Cardiol. 174 (2) (2014) 337–342.
[22] W.L. Beaver, K. Wasserman, B.J. Whipp, A new method for detecting anaerobic threshold by gas exchange, J. Appl. Physiol. (1985) 60 (6) (1986) 2020–2027.
[23] K.H.J. Wasserman, D.Y. Sue, W.W. Stringer, B.J. Whipp, Principles of Exercise Testing and Interpretation: Including Pathophysiology and Clinical Applications, fifth ed. Lippincott Williams and Wilkins, Philadelphia, 2012.
[24] P.G. Camici, F. Crea, Coronary microvascular dysfunction, N. Engl. J. Med. 356 (8) (2007) 830–840.
[25] B.K. Lee, H.S. Lim, W.F. Fearon, et al., Invasive evaluation of patients with angina in the absence of obstructive coronary artery disease, Circulation 131 (12) (2015) 1054–1060.
[26] C.J. Pepine, K.C. Ferdinand, L.J. Shaw, et al., Emergence of nonobstructive coronary artery disease: a woman's problem and need for change in definition on angiography, J. Am. Coll. Cardiol. 66 (17) (2015) 1918–1933.
[27] C. Zuchi, I. Tritto, G. Ambrosio, Angina pectoris in women: focus on microvascular disease, Int. J. Cardiol. 163 (2) (2013) 132–140.
[28] J.P. Halcox, W.H. Schenke, G. Zalos, et al., Prognostic value of coronary vascular endothelial dysfunction, Circulation 106 (6) (2002) 653–658.
[29] C.J. Pepine, R.D. Anderson, B.L. Sharaf, et al., Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) study, J. Am. Coll. Cardiol. 55 (25) (2010) 2825–2832.
[30] R. Sicari, F. Rigo, L. Cortigiani, S. Gherardi, M. Galderisi, E. Picano, Additive prognostic value of coronary flow reserve in patients with chest pain syndrome and normal or near-normal coronary arteries, Am. J. Cardiol. 103 (5) (2009) 626–631.
[31] G.O. von Mering, C.B. Arant, T.R. Wessel, et al., Abnormal coronary vasomotion as a prognostic indicator of cardiovascular events in women: results from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE), Circulation 109 (6) (2004) 722–725.
[32] M. Naya, N. Tamaki, H. Tsutsui, Coronary flow reserve estimated by positron emission tomography to diagnose significant coronary artery disease and predict cardiac events, Circ. J. 79 (1) (2015) 15–23.
[33] J. Wohrle, T. Nusser, N. Merkle, et al., Myocardial perfusion reserve in cardiovascular magnetic resonance: correlation to coronary microvascular dysfunction, J. Cardiovasc. Magn. Reson. 8 (6) (2006) 781–787.
[34] M. Gulati, D.K. Pandey, M.F. Arnsdorf, et al., Exercise capacity and the risk of death in women: the St James Women Take Heart Project, Circulation 108 (13) (2003) 1554–1559.
[35] R.K. Hung, M.H. Al-Mallah, J.W. McEvoy, et al., Prognostic value of exercise capacity in patients with coronary artery disease: the FIT (Henry Ford ExercIse Testing) project, Mayo Clin. Proc. 89 (12) (2014) 1644–1654.
[36] S. Kodama, K. Saito, S. Tanaka, et al., Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis, JAMA 301 (19) (2009) 2024–2035.
[37] J. Myers, M. Prakash, V. Froelicher, D. Do, S. Partington, J.E. Atwood, Exercise capacity and mortality among men referred for exercise testing, N. Engl. J. Med. 346 (11) (2002) 793–801.
[38] J.H. Mieres, G.V. Heller, R.C. Hendel, et al., Signs and symptoms of suspected myocardial ischemia in women: results from the What is the Optimal Method for Ischemia Evaluation in WomeN? Trial, J. Women's Health (Larchmt) 20 (9) (2011) 1261–1268.
[39] T. Kavanagh, D.J. Mertens, L.F. Hamm, et al., Prediction of long-term prognosis in 12 169 men referred for cardiac rehabilitation, Circulation 106 (6) (2002) 666–671.
[40] M.J. Joyner, D.J. Green, Exercise protects the cardiovascular system: effects beyond traditional risk factors, J. Physiol. 587 (Pt 23) (2009) 5551–5558.