Virginia Commonwealth University
VCU Scholars Compass

Theses and Dissertations

Graduate School

2010

The Clinical Utility of Cardiopulmonary Exercise Testing in Patients With Suspected Myocardial Ischemia

Sherry Pinkstaff
Virginia Commonwealth University

Follow this and additional works at: http://scholarscompass.vcu.edu/etd

Part of the Physiology Commons

© The Author

The Use of Cardiopulmonary Exercise Testing in Patients with Suspected or Confirmed Myocardial Ischemia

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

Sherry Pinkstaff, PT, DPT
Doctor of Philosophy
Dissertation Advisor: Ross Arena, PhD, PT
School of Allied Health, Department of Physical Therapy

August 11, 2010

Acknowledgement

It is true that one does not pursue a PhD in isolation, without the help of many others who may share in the successes and failures. However it can also be a lonely endeavor. Throughout the process I needed not only the people who provided ongoing, at times, daily guidance, but also those who supported me simply by believing in me and loving me. For the former, my mentor Ross Arena was indispensible. I owe him more than I could ever repay but I will spend the rest of my career attempting to live up to the very high standard he has set. For the latter, my husband was invaluable. My happy marriage remains the achievement I am most proud of, despite this or any other personal success.

Table of Contents

CHAPTER	TITLE	PAGE

List of Abbreviations

APMHR	Age Predicted Maximum Heart Rate
AT	Anaerobic Threshold
ATP	Adenosine Triphosphate
AUC	Area Under Curve
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CO	Cardiac Output
CPX	Cardiopulmonary Exercise Test
CT	Computed Tomography
DBP	Diastolic Blood Pressure
DTS	Duke Treadmill Score
ECG	Electrocardiogram
EDV	End Diastolic Volume
EF	Ejection Fraction
EIMI	Exercise Induced Myocardial Ischemia
ESV	End Systolic Volume
HF	Heart Failure
HR	Heart Rate
LV	Left Ventricle (Or Ventricular)
MET	Metabolic Equivalent
MI	Myocardial Infarction

MPI (MPS)	Myocardial Perfusion Imaging (Myocardial Perfusion Study)
MUGA	Multigated Acquisition Radionuclear Angiography
OUES	Oxygen Uptake Efficiency Slope
PTCA/PCI	Percutaneous Transluminal Coronary Angioplasty/Percutaneous Coronary Intervention
RCT	Respiratory Compensation Threshold
RER	Respiratory Exchange Ratio
RPP	Rate Pressure Product
SBP	Systolic Blood Pressure
SPECT	Single Photon Emission Computed Tomography
SV	Stroke Volume
TM	Treadmill
VCO_2	Ventilatory Carbon Dioxide Production
VE	Minute Ventilation
VO_2	Ventilatory Oxygen Consumption
VT	Ventilatory Threshold
WR	Work Rate

List of Tables and Figures

Abstract

THE CLINICAL UTILITY OF CARDIOPULMONARY EXERCISE TESTING IN PATIENTS WITH SUSPECTED MYOCARDIAL ISCHEMIA

Sherry Osborn Pinkstaff, PhD, DPT

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

Virginia Commonwealth University, 2010

Dissertation Advisor: Ross A. Arena, PhD, PT
School of Allied Health, Department of Physical Therapy

Heart disease is a major cause of morbidity and mortality in the United States with coronary artery disease (CAD) representing more than half of all cardiovascular events. Stable patients presenting with symptoms suggestive of CAD are likely to undergo either an exercise ECG and/or imaging study as a first line diagnostic assessment. A cardiopulmonary exercise test (CPX) is an ECG stress test plus ventilatory gas analysis. Recently CPX has been used to detect exercise-induced myocardial ischemia suggestive of underlying CAD. Currently there are a number of diagnostic tests available for the identification of CAD with the most widely used being exercise ECG, myocardial perfusion imaging (MPI) and cardiac catheterization. Exercise ECG, although inexpensive, has a number of well-recognized limitations, including low sensitivity resulting in false positive results. MPI and catheterization are more accurate but also more invasive and expensive. It appears that CPX may improve the diagnostic accuracy of exercise ECG in a cost effective manner. This dissertation consists of one literature review and

two original papers that will address the utility of CPX in patients being evaluated for possible myocardial ischemia.

Introduction

Cardiovascular disease is expensive and the cost is paid in lives lost and dollars spent. Indeed, the number of Americans with some form of heart disease is staggering. In 2005 the prevalence of heart disease in the US was nearly 81 million, and the prevalence of stroke nearly 6 million. Although primarily a metabolic disorder, the leading cause of death in patients with diabetes is cardiovascular disease and in 2005 the combined prevalence of diabetes and pre-diabetes was nearly 75 million. The annual cost of cardiovascular disease in the US is approximately $450 billion and accounts for more than 1/3 of all deaths, with almost 2400 each day. [1]

Coronary artery disease (CAD) makes up more than half of all the cardiovascular events in men and women 75 years or younger.[1] A large percentage of the costs associated with CAD are for diagnosis and evaluation, including those for the determination of disease severity and efficacy of treatment. Clinicians use a mix of invasive and non-invasive tests with a wide range of costs to evaluate patients with suspected or confirmed CAD. An estimated 7 million inpatient cardiovascular operations and procedures are performed each year and cardiac catheterization, the gold standard diagnostic tool for the detection of coronary artery stenosis, represents nearly 1.6 million of those. The mean charge for patients hospitalized for this procedure increased from $11,611 in 1993 to $26,910 in 2005.[1]

Cardiac catheterization is usually the first test to be performed in a patient with symptoms of an acute myocardial infarction. Stable patients presenting with symptoms suggestive of CAD are more likely to undergo either an exercise ECG (the typical "stress test") and/or an imaging study (myocardial perfusion imaging or echocardiography) as a first line diagnostic assessment. Many of these rely on the use of either exercise or pharmacological stress to sufficiently augment

myocardial oxygen demand. In addition to recording the ECG response, the stress portion of the test is used primarily to achieve the appropriate heart rate to assure diagnostic accuracy of the imaging study and typically none of the exercise data is considered in the final analysis.

However, it is known that assessing the hemodynamic response to exercise, such as heart rate recovery[2], yields powerful clinical information and the same is true for information gained from ventilatory gas analysis. A cardiopulmonary exercise test (CPX) is one with ECG monitoring plus ventilatory gas analysis. That is, during the test all of the air inspired and expired by the patient is collected and analyzed. CPX has been widely applied to the evaluation of heart failure where it is routinely used to determine disease severity and prognosis.[3-8] It is also well-recognized for its ability to differentiate between cardiac and pulmonary causes of unexplained dyspnea. [9-12] Furthermore, CPX is increasingly utilized in the diagnosis of pulmonary hypertension.[13-15] See Table 1 for a full listing of the current clinical indications for CPX.

Recently CPX has begun to emerge as a tool to diagnose CAD but there remain unanswered questions. Therefore, this review will discuss the use of CPX in the identification of suspected or confirmed CAD. First, a description of the principles of exercise physiology relevant to CPX will be presented. Next, normal and abnormal myocardial physiology will be described, including the pathophysiology of CAD and the rationale for the use of CPX in detecting exercise-induced myocardial ischemia (EIMI). The most frequently applied diagnostic tools will be briefly presented with a focus on their diagnostic accuracy. Finally a literature review will provide the reader with a sense of what has been demonstrated to-date followed by a discussion of how this body of evidence might be advanced.

Exercise Physiology and Exercise Testing Review

A detailed description of the CPX instrumentation needed for data collection and analysis is beyond the scope of this review however a brief overview is provided in Figure 1. What is vital to understanding the physiological basis for CPX is the interconnectedness of the cellular, pulmonary, and cardiovascular mechanisms involved in the acute exercise response. Oxygen is the primary molecule involved in the creation of adenosine triphosphate, the major fuel source necessary for all metabolic work. At rest the cardiopulmonary system works in a coordinated fashion to deliver adequate oxygen to fuel the cellular respiration underlying the conversion of chemical energy to mechanical energy. Almost immediately upon the initiation of exercise, the demand for ATP increases, increasing the demand for oxygen and causing a greater ventilatory drive. Thus, oxygen consumption (VO_2) can be thought of as a surrogate for cellular activity. The Fick Equation describes the acute physiological response to exercise:

$$Q = VO_2/\text{arterial} - \text{venous } O_2 \text{ difference}$$

Q represents cardiac output and is the central (i.e. cardiac) contribution to oxygen consumption (VO_2). The cardiovascular system couples to the respiratory system by sensing the increase demand for oxygen and responds with a greater cardiac output (CO), the product of heart rate (HR) and stroke volume (SV). An increase in ventilation with exercise, and therefore an increased oxygen demand, must be matched by an increase in blood flow. Venous return is augmented by several mechanisms. First, venous constriction results in a greater preload and therefore an increased CO. This causes a dilatation of the pulmonary capillaries providing blood flow to alveoli previously un- or under perfused. At the same time, blood flow to the working skeletal muscle is augmented by arterial vasodilation while splanchnic vasoconstriction shunts blood away from the abdominal viscera.[16]

Substituting HR * SV for Q gives the following:

$$HR * SV = VO_2/\text{arterial} - \text{venous } O_2 \text{ difference}$$

This final term represents the peripheral component of oxygen consumption, the arterial –

venous O_2 difference (a-vO_2 difference), which is the difference in oxygen content between the

veins and the arteries. At rest, oxygen extraction is approximately 30-40%. During exercise a

larger percentage of oxygen is unloaded from the blood into working skeletal muscles. Arterial

oxygen content (PaO_2) rises only slightly and the greater a-vO_2 difference is explained primarily

by decreased venous oxygen content (PvO_2) due to increased extraction by the metabolically

active muscles. Finally, what remains is the following rearrangement of the Fick equation,

which is the basis for CPX:

$$VO_2 = (HR * SV) * \text{a-v}O_2 \text{ difference}$$

Importantly, the largest contributor to maximal/peak VO_2 is maximal CO and positive or

negative alterations in the former are primarily explained by shifts in the latter. In addition to

VO_2, numerous other variables, both ventilatory and non-ventilatory, are collected during a

routine CPX. See Table 3 for a full listing of the most commonly assessed variables.

While a number of variables can be derived from ventilatory gas analysis, real-time tracking of

the O_2-pulse and change in VO_2/change in work rate ($\Delta VO_2/\Delta WR$) have been most thoroughly

investigated in subjects with suspected or confirmed myocardial ischemia. Normal and

abnormal responses for these CPX variables are illustrated in Figures 2 and 3, respectively.

Myocardial Oxygen Consumption

Like skeletal muscle, the myocardium depends on the generation of ATP for the

conversion of chemical energy into mechanical work. For optimal function myocardial

metabolism is primarily oxidative, with a preference for fatty acids in the fasted state and carbohydrate in the fed state. Analogous to whole body oxygen consumption ($VO_2 = CO * a\text{-}v$ O_2 difference) myocardial oxygen consumption is also determined by blood flow and oxygen extraction. Whereas resting oxygen extraction in skeletal muscle is quite low (30-40%), in some regions of the heart it is 70-80%. The functional consequence of this difference is that during exercise skeletal muscle has two ways to increase oxygen supply. The first is vasodilation (to increase delivery) and the second is increased oxygen extraction. The latter is largely not an option for the myocardium, especially the left ventricle. Thus, the only way to improve oxygen delivery is to increase blood flow.[17]

Blood flow to the heart is supplied by the coronary arteries which arise from the aorta just superior to its semilunar valve. Two main arteries, the left and right coronary arteries and their branches, supply all of the blood to the myocardium. Although there is a variation among humans the typical territory supplied by each epicardial artery can be generalized. The right coronary artery primarily supplies the right atrium and ventricle, the SA and AV nodes and part of the AV septum. It also may help to supply the left ventricle. The left coronary artery supplies the left ventricle and atrium, part of the right ventricle, the interventricular septum and sometimes the SA node.

Coronary blood flow at rest is determined by perfusion pressure and coronary resistance, with the latter being the largest contributor. Perfusion pressure is provided by aortic pressure at the outset and is impacted by the back pressure exerted by the contracting myocardium, called extravascular compression. This pressure is significant enough to cause a cessation or even a reversal of flow through the coronary arteries during systole at rest. Therefore at rest the coronary arteries are perfused during diastole. During exercise systolic filling is increased. This

is especially important under pathological conditions, especially hypertension and coronary artery disease. In both cases perfusion of the coronary arteries may become more difficult, exacerbating the consequences of the already-reduced flow.[18]

Coronary resistance is set not by the large epicardial coronary arteries, but rather by the small arteries and arterioles[19] and is determined by the diameter and length of the vessels, as well as the number of vessels in parallel, supplying a specific area of myocardium.[20] Vessel diameter can change in response to neural input, local metabolites, such as Angiotensin II, ATP and adenosine, and endothelium-derived vasoactive agents such as nitric oxide and endothelin.[21]

Autonomic influence on the heart is primarily neurally mediated however experiments in denervated hearts show that this is not the only mechanism. The heart is influenced by a variety of neurotransmitters working on different receptors including adrenergic and muscarinic. Parasympathetic control of the heart is mediated by acetylcholine which acts on muscarinic receptors to slow heart rate and reduce contractility and conduction velocity of the AV node and automaticity of the SA node. Alpha adrenergic influence is primarily vasoconstrictive and serves to reduce coronary blood flow. Beta adrenergic activation typically results in vasodilation and increased coronary blood flow.[22]

In accordance to their function, the four chambers of the heart require different amounts of oxygen. Myocardial oxygen consumption is greatest in the left ventricle (followed by the right ventricle and then the atria) and this is due to greater total blood flow and higher levels of oxygen extraction compared to the other chambers.[22] During exercise the increased myocardial oxygen demand is due mainly to an increase in heart rate[23, 24] contractility[25-29] and left ventricular work[28, 29]. During exercise, taking into account the constraining effect of the extravascular

9

compression forces, perfusion pressure is increased approximately 20-30%.[30] During exercise, change in resistance is the primary means by which blood flow is increased.[21]

Atherosclerosis and Coronary Artery Disease

Atherosclerosis is an inflammatory condition affecting primarily the intimal layers of medium to large coronary, cerebral and lower extremity arteries. Endothelial damage causes the accumulation of oxidized LDL and the recruitment of additional inflammatory agents which can themselves result in more injury and induce further vascular dysfunction.[31, 32] Atherosclerosis of coronary arteries has many consequences, including reduced blood flow to the myocardial territory supplied by that vessel. Under conditions of mild ischemia, preferential resting substrate utilization changes from fatty acid oxidation to glycolsysis. This represents the body's effort at improving efficiency because the oxidation of glucose requires fewer oxygen atoms per ATP produced (although fewer total ATP are formed). Concurrently fatty acid oxidation is inhibited resulting in accumulation of this cardiotoxic substrate. As ischemia proceeds the production of ATP is drastically reduced by this and by reduced glucose transport due to the low/no blood flow conditions.[17]

When a coronary artery is stenotic due to atherosclerosis there is increased perfusion pressure proximal and decreased perfusion pressure distal to the blockage. Once this situation reaches a critical level, defined as a 50-70% reduction in luminal diameter depending on the specific vessel, coronary flow reserve (maximum blood flow/basal blood flow) is reduced due to an increase in resistance across the affected artery. If post stenotic pressure falls below 40 mmHg the myocardium fed by that vessel will become under perfused and potentially hypoxic.[33-35] The effect of extravascular forces is exacerbated in the presence of a blockage,

especially in the face of high diastolic pressures or diastolic dysfunction.[22] At rest

homeostasis may be achieved, however during periods of physical exertion, the demand for

oxygen may outstrip the ability for it to be supplied.

Examination Techniques for the Diagnosis of CAD

The most widely used tools to diagnosis CAD rely on the assessment of coronary artery

physiology and/or anatomy, as described above. All of these methods have advantages and

limitations which impact their effectiveness. The following section describes the most

commonly used tests (exercise ECG, myocardial perfusion imaging, echocardiography and

cardiac catheterization) and introduces the potential utility of CPX. Table 4 provides details

related to costs, diagnostic accuracy and limitations.

The ECG has played a prominent role in the long history of the diagnosis of CAD. It is

considered a standard portion of any exercise test, one which does or does not utilize ventilatory

gas analysis. Pathological processes such as atherosclerosis can change the appearance of ECG

waveforms, in particular the QRS complex and the T wave. The ST segment is the portion of the

ECG waveform most often used in the diagnosis of ischemic disease and is defined as the end of

the QRS complex, called the J point, to a user defined interval, usually 0.08 seconds. Changes to

the ST segment manifests as elevation, depression or normalization. ST segment changes can

result from pathologies other than CAD, including valvular heart disease, congenital heart

disease, cardiomyopathy, and pericardial disorders. They are also associated with gender, some

pharmaceutical agents, electrolyte abnormalities, testing in a non-fasting state, electrical

conduction abnormalities and inadequate equipment.[16]

ST segment elevation is less common than depression and is believed to be indicative of more severe transmural or epicardial ischemia and possibly localizable to the myocardial area from which it is recorded. There is some debate on whether elevation is reflective of ischemia or wall motion abnormalities and the answer may be dependent on the cardiac history of the subject. ST segment depression is the most common ECG change associated with EIMI and its physiological basis is subendocardial ischemia. The ECG leads in which it appears are not reflective of the location of the ischemia or the arteries affected. ST depression can be down sloping, horizontal, or up sloping with severity being greatest in the first followed by the second and third. However, the amount and slope of the depression are related to the probability and severity of disease. ST segment changes appearing only in recovery from exercise appear to be of some clinical value.[16]

The diagnostic accuracy of the exercise ECG stress test has been thoroughly reported in the literature. The primary limitation is that various cardiac pathologies affect conduction, and therefore the appearance of the ECG. Additionally, the ST segment appears to be differentially impacted by gender with more women demonstrating conduction patterns suggestive of ischemia at rest. In one large meta-analysis that included nearly 150 studies and approximately 24,000 subjects, Gianrossi[31] reported the range of sensitivity to be 23-100% (mean 68%) and the specificity to be 17-100% (mean 77%). A separate analysis excluding those with a history of myocardial infarction resulted in a reduction of the mean specificity to 74%. Similar reductions in diagnostic accuracy are found when the effects of digoxin, left ventricular hypertrophy and resting ST depression are removed from the analysis.[16]

From 1993-2001 the use of non-imaging stress tests, such as exercise ECG, declined in all groups except black males. During the same period the use of imaging stress tests, for

example myocardial perfusion imaging and echocardiography, increased from as low as 20 per 1000 (black females) to as many as 100 per 1000 (nonblack males).[32] Myocardial perfusion imaging (MPI) has become the most commonly employed imaging test for the detection of stable coronary artery stenosis.[33] This technique uses radioactive tracers (thallium or technetium are the two most common) and imaging, via single photon emission computed tomography (SPECT), to identify hypoperfused regions of myocardium. The myocardium will take up these tracers to the same level if all areas are equally perfused. Areas with reduced blood flow, either at rest or during stress (exercise or pharmacologically-induced), will exhibit areas of attenuation. If no attenuation is evident on the stress images, acquiring rest images is considered by most to be superfluous. The addition of ECG gating (ECG-gated SPECT) allows the nuclear perfusion study to also capture data on LV wall motion, thickness and function.

The diagnostic accuracy of MPI SPECT is reported in the range of 87-89% for sensitivity and 73-75% for specificity. Accuracy is impacted by the extent of previous myocardial injury, the presence of resting perfusion abnormalities without the benefit of a "normal" comparison and poor imaging quality due to adiposity or other patient characteristics. Additionally, for pharmacologically-induced stress studies, perfusion abnormalities might not correlate well with functional limitations.

Another imaging test, stress echocardiography, uses rest and stress images to detect changes in wall motion, wall thickness and LV function to identify ischemia.[33] The stress can be exercise or pharmacologically-induced, although it appears diagnostic accuracy is improved with the former. Exercise echocardiography has been shown to be especially effective in women and those with baseline conduction abnormalities who have a high rate of false positive ECG findings. In these patients echocardiography may also be more cost-effective.[34-36] One

limitation of echocardiography is obtaining images when the visual field is obstructed by adiposity or other anatomical obstruction.

At the far end of the invasiveness spectrum is cardiac catheterization, the gold standard for detection of coronary artery stenosis.[33, 37] However, limitations exist, chief among them being the lack of correlation between structure and function. That is, luminal narrowing may be present in the absence of symptoms or symptoms may be present in the absence of obvious stenosis.[38] Furthermore catheterization carries risks of adverse events the treatment of which, even if they are minor, adds to the already steep cost of the procedure. For this reason and others, catheterization should only be performed in patients with a high pre-test probability of having CAD. In this way catheterization serves the role of confirming disease and providing the gateway to immediate intervention more so than providing an initial diagnosis for those with stable CAD.

Additional tests for the detection of clinically significant stenosis include cardiac MRI, and computed tomography (CT). Although a detailed description of these methods is beyond the scope of this review because of their lack of widespread use, information related to their diagnostic accuracy is included in Table 4.

The power of CPX to identify EIMI lies in its acute sensitivity for detecting changes in oxygen consumption and carbon dioxide production in real-time. It may be especially well-suited to the consequences of myocardial ischemia because of the absolute reliance of cardiac muscle on oxygen. That is, during exercise the demand for oxygen is directly related to the demand for ATP. If this demand is not met, ATP production will fall and subsequently contractility will suffer. Left ventricular dysfunction will nearly instantly ensue reducing the heart's pumping ability. Cardiac output will be diminished reducing oxygen delivery to the

working skeletal muscle and whole body oxygen consumption will fall. Not only will systemic circulation be affected, but pulmonary circulation, too. Delivery of blood back to the heart will also suffer, reducing expired carbon dioxide. These consequences will be reflected in many of the variables assessed with CPX.

Literature Review for CPX use in Detecting EIMI

The use of CPX in the evaluation of CAD began at least 30 years ago with research linking the effects of myocardial infarction with left ventricular (LV) function and has progressed to the more generalized condition of reduced myocardial blood flow. More recently, several investigations have used oxygen consumption as a surrogate for real-time cardiac output to describe the acute consequences of exercise-induced ischemia. To-date, very few studies have reported on the use of CPX as a primary tool to diagnose myocardial ischemia. However, there is an apparent evolution in the literature beginning with attempts to understand LV function, progressing to the analysis of ventilatory gas as a marker of underlying myocardial ischemia and finally descriptions of the effects of specific pharmaceutical agents or surgical intervention on LV function and exercise capacity. These investigations have been limited in scope but hint at the potential utility of CPX in the diagnosis of CAD. The following is a description of those studies (additional details can be found in Table 5)

Investigations Using Exercise Testing/CPX to Diagnose CAD

In 1980 Upton et al[39] built on work demonstrating LV dysfunction after coronary artery ligation in an animal model. On this principle, the temporal relationship between LV function, and angina and ST segment changes in a group of patients with CAD was investigated. This

15

important study demonstrated the presence of LV dysfunction prior to the onset of angina or ST segment changes. The LV dysfunction during exercise was characterized as a decrease or a less than 5% increase in ejection fraction (EF), a greater than 25% increase in end diastolic volume (EDV) or an increase in end systolic volume (ESV). Ehsani et al [40] confirmed Upton's finding of a decrease in EF during exercise in patients with asymptomatic CAD (silent ischemia) which was significantly correlated with other CPX variables. In this study all patients had a normal EF at rest. During exercise some patients had an increase in EF while others experienced a decline. In those with a decrease, O_2-pulse was also significantly lower, as was total exercise time, HR_{max} and VO_{2max}. This work also confirmed earlier findings that resting EF was not significantly correlated with exercise capacity (VO_{2max}), however there was a weak but significant correlation between VO_{2max} and peak EF.

Koike et al[41] demonstrated in a heterogeneous heart disease population that the anaerobic threshold correlated with the VO_2 above which LV function deteriorated [as evidence by a decrease in EF, ESV, and cardiac output/work rate (CO/WR)]. He then expanded on this work in a group of patients with a history of myocardial infarction.[42] Previous work had demonstrated a linear relationship between VO_2 and WR ($\Delta VO_2/\Delta WR$) in normal, healthy subjects and a reduction of this slope in those with CAD. While Koike failed to confirm this finding; he did report a flattening of the slope of both CO/WR and CO/VO_2. The explanation offered was that an increase in oxygen extraction might be able to explain the preservation of the $\Delta VO_2/\Delta WR$ slope. On the other hand, only LV dysfunction could explain the decrease in $\Delta CO/\Delta VO_2$ above the anaerobic threshold.

Koike[43] further contributed to this body of literature with a study demonstrating important differences in the oxygen uptake kinetics in patients with prior MI. Oxygen uptake

kinetics refers to the speed at which VO_2 increases when exercise is initiated. Faster kinetics is indicative of a healthier cardiovascular system. Koike showed that prolonged kinetics is directly related to low cardiac output in patients with LV dysfunction.

In the mid-late 1990's several more researchers began focusing on this question. In 1995 Meyer et al[44] compared the ischemic and ventilatory threshold (VT). The ischemic threshold (IT) is the point at which ST segment changes and/or angina appears during exercise whereas VT is the point where there is an increased reliance on anaerobic metabolism. The study confirmed the earlier findings about the appearance of ventilatory markers occurring prior to ECG markers of ischemia. However this paper disputes the conclusion that the ventilatory changes are reflective of central, or left ventricular, origin and proposes that it is the peripheral contribution to exercise capacity that determined the shift toward a higher reliance on anaerobic metabolism. To support this they administered isosorbide dinitrate and found no changes in VO_2, O_2 pulse, lactate, HR or rate pressure product at the VT. On the other hand, at the IT, all of these variables were significantly improved. The authors explain this by suggesting the patients were deconditioned due to their disease and/or sedentary lifestyle.

Klainman et al[45] continued on in relating ventilatory variables to LV function in a study of patients with and without symptomatic ischemia (i.e. symptomatic vs. silent) but no previous history of MI or cardiac surgery. This group was compared to a control group without ECG evidence of ischemia. Several CPX variables were considered and LV function (via EF) was assessed with multigated acquisition radionuclear angiography (MUGA), the gold standard assessment for determination of EF. VO_{2max} and O_2-pulse were lower in both ischemic groups (symptomatic and silent) compared to the controls. These two variables were also significantly lower in the symptomatic ischemia group compared to the silent ischemia group. Moreover, in

the symptomatic ischemia group there was a significant reduction in EF during exercise however in both other groups the EF increased. This study offers support not only to the correlation between LV function and CPX variables but also to the belief that in non-diabetics silent ischemia represents less significant disease.

An important contribution to this growing body of literature was made by an investigation reporting on the link between diastolic dysfunction and exercise capacity.[46] In a group of patients with known CAD whose chief complaint was dyspnea it was demonstrated that at peak exercise the time-to-peak filling was significantly increased and correlated with exercise capacity (VO_{2max}). The authors posit that diastolic dysfunction could lead to systolic dysfunction accounting for the reduced cardiac output demonstrated in earlier studies.

Another paper from Klainman's lab[47] reported on 50 patients with CAD without a previous history of myocardial infarction who underwent a CPX followed by a myocardial perfusion study (ECG-gated SPECT) to determine the relationship between extent of ischemia and aerobic capacity. In it, patients with global ischemia <20% were significantly different than those at levels >20% in terms of VT, maximal work load achieved, max predicted HR, percent predicted VO_2, VO_{2max} and $\Delta VO_2/\Delta WR$, despite no differences in number of stenotic arteries, extent of ST depression or presence of angina. The only SPECT markers that were significantly different between the two groups (<20% vs >20%) were increase pulmonary uptake and transient ventricular dilatation, both of which the authors note are consequences of exercise-induced ischemia.

Bigi et al[48] used estimates of CO and measured VO_2 to identify a cut point able to discriminate between those with and without CAD. Sensitivity, specificity, negative and positive predictive value were all improved upon by the analysis of CPX variables [CO at ventilatory

threshold (CO_{VT}), to be specific] vs. ECG changes. Moreover, three CPX variables (CO_{VT}, VO_2 at VT and peak VO_2) were shown to be prognostic of future adverse cardiac events in the same patient population.   Furthermore, a cut off value of 7.3 L/min for CO_{VT} predicted improved survival whereas the same was not true for the presence or absence of ECG changes.

Starting in the 2000's focus began to shift to specific CPX variables, in particular O_2-pulse and the slope of $\Delta VO_2/\Delta WR$, in detecting myocardial ischemia. Specifically, Klainman[49] attempted to create a scoring system for the common changes seen in the behavior of the O_2-pulse during exercise in those with and without ischemia. O_2-pulse behavior was observed for normal linearity, flattening or decreasing slope during exercise. Using this scoring system, it was possible to distinguish between CAD patients with or without impaired LV function as quantified by MUGA.

Belardinelli et al[50] prospectively studied a large group of patients with confirmed CAD and compared the results of CPX and ECG to SPECT. By logistic regression the independent predictors of a positive nuclear perfusion study were duration of O_2-pulse flattening and flattening of the slope of $\Delta VO_2/\Delta WR$. The addition of both of these positive findings significantly improved the sensitivity and specificity of the ECG findings. Importantly, the addition of CPX helped to rule out ischemia in a significant portion of individuals for whom the ECG was falsely positive. False positive ECG findings are especially problematic because they are more prevalent in women and because of the additional expense and risk incurred by additional testing. Bussotti failed to confirm these O_2-pulse findings but did affirm that a flattening of $\Delta VO_2/\Delta WR$ relationship in addition to low VO_2 values at both the VT and IT as being suggestive of myocardial ischemia.[51]

Munhoz et al[52] attempted to validate the findings regarding O_2-pulse in a mode-independent manner. That is, most of the previous investigations had been performed on a bicycle ergometer and it was unknown if the phenomenon would remain diagnostic if the CPX was conducted on a treadmill. All patients had a history of diagnosed CAD. Oxygen pulse was assessed as an absolute value and compared in the group with ischemia vs. without and a separate comparison was made in a group with mild vs. extensive ischemia. Only in the confirmed ischemia group was a significantly lower O_2-pulse observed.

Studies Evaluating CPX Variables after Coronary Intervention

Several studies starting in the late 1980's evaluated the effect of percutaneous transluminal coronary angioplasty (PTCA) on the CPX response. Ajisaka et al[53] demonstrated a significantly increased VE/VCO$_2$ slope above the respiratory compensation point (i.e. the anaerobic threshold) between patients with CAD with normal EF and controls. The minute ventilation/carbon dioxide production (VE/VCO$_2$) slope improved (i.e. was reduced) after intervention with PTCA but only in patients for whom the PTCA was successful. In those with failed PTCA, the VE/VCO$_2$ slope actually increased further, suggesting these patients were suffering worsening cardiac function. Klainman et al[54] reported on 29 patients who performed a CPX before and after PTCA, after which significant improvements were noted in O_2-pulse, VO$_2$, O_2-pulse score and the ventilatory anaerobic threshold. Adachi et al[55] reported a significant reduction in the time constant of VO$_2$ kinetics following PTCA. The oxygen kinetic response has been linked to cardiac output and the authors argue that an improved time constant is due to the improved cardiac output following intervention. For patients with failed PTCA, the speed of the O_2 kinetic response was no different than at their first CPX. Most recently, Inbar et al[56]

confirmed these findings. Two groups were compared, the first of which underwent PTCA while none of the second did. All subjects performed a CPX twice. Only in the intervention group did peak VO_2, VO_2 at VT, peak O_2-pulse, and the O_2-pulse slope improve significantly. Moreover, the diagnostic accuracy of CPX to demonstrate this change was superior to ECG.

Two single patient case studies of right coronary artery disease reported the findings of a significant flattening in O_2–pulse and the $\Delta VO_2/\Delta WR$ relationship which normalized after PTCA.[57, 58]

Studies Evaluating CPX Variables after Pharmaceutical Intervention

Finally, several investigators are beginning to use CPX variables to demonstrate improved LV function following pharmaceutical intervention. For example, the mechanism of action for trimetazidine is a shift is substrate utilization toward glucose and away from fatty acids, which would be beneficial to myocardium facing an O_2 supply-demand mismatch. This shift enables a higher yield of ATP for oxygen consumption and results in improved contractility without an effect on heart rate or blood pressure. In patients with ischemic cardiomyopathy, trimetazidine has been shown to improve LV function, as demonstrated by improvements in peak VO_2, without hemodynamic effects.[59] Further, the addition of this drug potentiates the effect of exercise in a group of patients with ischemic cardiomyopathy.[60] Similarly, pyridostigmine bromide, a cholinesterase inhibitor had a positive effect on exercise capacity as demonstrated by a delay in the onset of ischemia, increased peak VO_2 and peak O_2 pulse.[61] Lastly, the effect of coenzyme Q_{10} (CoQ_{10}) on cardiovascular function and CPX variables has been investigated.[62] CoQ_{10} has been demonstrated to be an antioxidant, have the ability to improve mitochondrial

bioenergetics and counteract endothelial dysfunction. In CoQ_{10} supplemented patients peak VO_2 and O_2-pulse were improved versus controls.

Gaps in the Literature

As is demonstrated by the progression and scope of these studies CPX variables accurately reflect LV function and furthermore, specific and predictable changes to CPX variables are indicative of EIMI. Despite this body of promising preliminary evidence, the question remains if CPX can be used clinically to improve the diagnostic accuracy of the standard ECG exercise test for the purpose of ensuring the appropriate follow up. In other words, can the addition of ventilatory gas analysis result in fewer patients undergoing unnecessary diagnostic tests? Beyond that, it will take additional research to determine if this approach is cost effective, resulting in better outcomes for patients.

Reducing work-up bias is a requirement for the evaluation of diagnostic tools but this is often overlooked in the methodologies of many studies.[63] Work up bias underestimates the specificity and overestimates the sensitivity. In many of the studies evaluating CPX the subjects had a previous diagnosis of coronary artery disease. To establish the diagnostic utility of CPX it will be important to validate these findings in a population of all subjects with undiagnosed CAD.

Furthermore, many of the studies described above used a bicycle ergometer as the mode of exercise, the more common mode in non-US countries. Additionally, the analysis of some of the CPX variables differs depending on the mode, requiring adjustments to be made. It must be demonstrated that the adjusted variables are also changed predictably in subjects who develop EIMI.

Lastly, a limited number of variables have been investigated, relative to those that can be obtained from a CPX, such as VE/VCO$_2$ slope and the partial pressure of end-tidal carbon dioxide (P$_{ET}$CO$_2$). Only one study reported on the changes in VE/VCO$_2$ slope induced by ischemia[53] and none have considered P$_{ET}$CO$_2$. There is good reason to believe that these variables will also change as ischemia brings on LV dysfunction and cardiac output decreases. For example, P$_{ET}$CO$_2$ is defined as the partial pressure of CO$_2$ at the end of exhalation and reflects the heart's ability to deliver deoxygenated blood back to the lungs. Indeed, in patients with heart failure, P$_{ET}$CO$_2$ is predictably low during exercise and at rest as one would expect with reduced CO.[64, 65] One would expect to see a normal rise in P$_{ET}$CO$_2$ followed by a decrease as the ischemic threshold is reached.

Conclusion

There are currently many commonly used tools to diagnose CAD and each has excellent diagnostic accuracy with sensitivities and specificities in the range of approximately 80-90%. The newest tests which are not yet incorporated into clinical practice to the same extent, such as cardiac MR or CT, incrementally improve upon this already impressive record. However, they do very little to reduce cost or chance of adverse event. In other words, there already exist many tests which all provide approximately the same information with the same or similar level of risk. What would be especially useful is improving on the accuracy of the inexpensive non-invasive test in order to direct patients to the next level of care more effectively. This is the potential role for CPX as it adds only incrementally to the cost but provides a substantial improvement in the accuracy of the common ECG exercise test. Furthermore there is the added benefit of obtaining

prognostic information and the opportunity to begin patient education regarding the importance of exercise.

Currently chest pain represents only 5% of the referrals for CPX and the barriers to fully integrate it into the routine diagnostic work-up of suspected CAD are significant.[66] Clearly more studies validating and expanding on the work that has already been done are needed. This additional research will support overcoming another impediment which is reimbursement from 3rd party payors such as Medicare. The use of CPX in the assessment of patients with heart failure is currently reimbursable, explaining in part its greater incorporation into clinical practice in this chronic disease population.

In order to realize the full potential of CPX the following recommendations are provided: 1) validate the findings of the preliminary investigations in a larger population of patients without work up bias 2) investigate other ventilatory markers of ischemia that may improve further on its diagnostic accuracy and 3) conduct a longitudinal study to evaluate the cost effectiveness of using CPX in the initial diagnosis of CAD.

Table 1: American College Of Cardiology/American Heart Association Guidelines For Cardiopulmonary Exercise Testing (Adapted from ATS/ACCP Statement on Cardiopulmonary Exercise Testing)[67]

Class (Indication)

I (indicated)

- Evaluation of exercise capacity and response to treatment in patients with heart failure who are being considered for heart transplantation

- Assistance in the differentiation of cardiac versus pulmonary limitations as a cause of exercise-induced dyspnea or impaired exercise capacity when the cause is uncertain

IIa (good supportive evidence)

- Evaluation of exercise capacity when indicated for medical reasons in patients for whom the estimates of exercise capacity from exercise test time or work rate are unreliable

IIb (weak supportive evidence)

- Evaluation of the patient's response to specific therapeutic interventions in which improvement of exercise tolerance is an important goal or end point

- Determination of the intensity for exercise training as part of comprehensive cardiac rehabilitation

III (not indicated)

- Routine use to evaluate exercise capacity

Table 2: Absolute and Relative Contraindications to Maximal Exercise Testing[68]

Absolute

- Acute myocardial infarction

- High-risk unstable angina

- Uncontrolled cardiac arrhythmias causing symptomatic or hemodynamic compromise

- Symptomatic severe aortic stenosis

- Uncontrolled symptomatic heart failure

- Acute pulmonary embolus or pulmonary infarction

- Acute myocarditis or pericarditis

- Acute aortic dissection

Relative

- Left main coronary stenosis

- Moderate stenotic valvular heart disease

- Electrolyte abnormalities

- Severe arterial hypotension

- Tachyarrhythmias or bradyarrhythmias

- Hypertrophic cardiomyopathy and other forms of outflow tract obstruction

- Mental or physical impairment leading to inability to exercise adequately

- High degree atrioventricular block

Table 3: Common Variables Assessed with CPX and their Physiological Significance

	NON-VENTILATORY GAS VARIABLES ASSESSED WITH CPX AND PHYSIOLOGICAL SIGNIFICANCE		
VARIABLE	**DEFINITION AND PHYSIOLOGICAL SIGNIFICANCE**	**NORMAL RESPONSE**	**ABNORMAL RESPONSE**
Heart Rate	The heart rate response to exercise is due to the autonomic nervous system. At rest the heart is under parasympathetic control. An increase in heart rate requires the the addition of sympathetic input. The return of heart rate to the resting value requires a reversal of this process.	Cardiovascularly fit individuals are able to achieve a higher percentage of their age predicted maximum heart rate.	A failure to achieve >85% maximum predicted HR, called chronotropic incompetence (CI), may be the result of ischemic limitation. Impaired autonomic function has been implicated in CI and prolonged heart rate recovery is consistently shown to be an indicator of poor prognosis.
Systolic BP	During exercise, systolic blood pressure (SBP) rises due to the increase in stroke volume and cardiac output. The strong muscular wall of the aorta into which the volume is being ejected has a constraining influence on cardiac output.	SBP increases with increasing work load during exercise and often returns to below baseline values for several hours following the cessation of exercise.	A blunted SBP increase is associated with cardiovascular disease, in particular CAD and heart failure, and confers poor prognosis. A decrease from baseline in SBP is associated with cardiovascular disease. Although CAD is often the cause, other explanations include peripheral vasodilation and mitral regurgitation.
Diastolic BP	Diastolic BP (DBP) is correlated with total peripheral resistance (TPR), which is the total resistance in the arterial system.	During exercise, DBP remains stable or decreases slightly due to the opposing influences of local muscle vasodilation and cardiac output.	A significant increase in DBP is associated with myocardial ischemia or may be a marker for labile hypertension, a risk factor for CAD development.
Dyspnea	Dyspnea is shortness of breath or increased work of breathing. Its physiological significance in heart disease is debated but may be related to systolic or diastolic dysfunction, ischemia or abnormal peripheral vascular tone.	Dyspnea can be a normal physiological consequence of heavy exertion, but it usually not exercise-limiting.	In one study of nearly 18,000 patients dyspnea, in the presence or absence of CAD and/or angina, was prognostic of future mortality from cardiac and non-cardiac causes.[69]
Angina	Chronic stable angina is the most common symptomatic manifestation of obstructive CAD. However, clinically significant CAD may be present in a patient not experiencing angina (so-called, silent or asymptomatic ischemia.) Causes of angina, other than CAD, are however numerous.	None	Typical angina is pressure, tightness, and/or diffuse pain located substernally, is centered in the neck or radiates down the left arm. It comes on with exertion and abates with rest.[16] In one study, 72% of the patients studied who developed chest pain with exercise but no ST segment changes had significant CAD identified angiographically.[70]

VENTILATORY GAS VARIABLES ASSESSED WITH CPX

VARIABLE	DEFINITION AND PHYSIOLOGICAL SIGNIFICANCE	NORMAL RESPONSE	ABNORMAL RESPONSE
VE	Minute ventilation (VE) is the volume (in liters) of air moving into and out of the lungs per minute and is the product of the respiratory rate and the volume of air exhaled with each breath, which generally is the same as the volume inhaled.	At rest, the respiratory rate is the primary determinant of VE. During exercise VE is augmented by an increase in tidal volume.	The ventilatory equivalent for O_2 (VE/VO$_2$) and CO_2 (VE/VCO$_2$) are often assessed and show characteristic changes in response to pathological states (see section below for more information on VE/VO$_2$ and VE/VCO$_2$.)
Anaerobic/ Ventilatory Threshold	Ventilation is driven by CO_2 levels. When cellular respiration is being primarily carried out aerobically, VE increases in near-perfect concert to allow for the elimination of the CO_2. As the contribution of anaerobic metabolism increases, ventilation will increase non-linearly to expel the additional CO_2 produced that cannot be buffered. This is called the anaerobic or ventilatory threshold (AT or VT).	A plot of ventilation and CO_2 production is linear below the AT/VT. Once this threshold is achieved, a steep increase in the slope of the line is noted. Beyond this threshold, exercise can only be maintained for a short period of time before reaching a maximum. A greater workload at a given anaerobic threshold is indicative of a fitter individual.	In less fit individuals and those with cardiovascular or pulmonary disease the AT will be reached at a lower workload. Clinically, the hemodynamic status of the patient at AT/VT has been shown to be important and clinical improvement often results in improvements in these values.
VO$_2$	VO$_2$ is the amount of O_2 removed from the inspired air, as it performs work. It is a direct measurement of aerobic exercise capacity. VO$_2$ has both central and peripheral components. Increases in VO$_2$ are explained primarily by increases in cardiac output.	In normal, non-diseased individuals, the cardiovascular system is the limiting factor to VO$_2$. That is, increases in VO$_2$ are limited by the heart's ability to deliver oxygen to the working muscles and not the lung's ability to participate in gas exchange. Absolute VO$_2$ is dependent primarily upon age and gender.	Reductions in exercise capacity are commonly seen in many diseases of the cardiovascular and pulmonary systems, as well as in those with general deconditioning due to sedentary lifestyle or chronic illness. In particular, a reduced peak or max VO$_2$ is associated with poor prognosis.[71]
Oxygen Pulse	Oxygen pulse (VO$_2$/HR) is an indirect measure of stroke volume	Under normal physiological conditions, O_2-pulse increases linearly with exercise and promptly falls upon cessation of exercise.	Several investigators have demonstrated a plateau or flattening of O_2-pulse in patients who develop myocardial ischemia during exercise. See Figure 2.
Respiratory Exchange Ratio	The respiratory exchange ratio (RER) is the ratio of VCO$_2$ to VO$_2$. At rest the body is utilizing (i.e. converting to CO_2) 75% of the oxygen it brings in, depending on the substrate being consumed. The RER for the complete oxidation of a carbohydrate is 1.0. As lipids are utilized the RER decreases because fats require more oxygen to be fully metabolized.	As exercise progresses, the production of CO_2 surpasses oxygen uptake and RER will exceed 1.0.[73] Although many factors contribute to RER this variable is the single best indicator of subject effort with a value ≥ 1.10 indicated maximal exertion.[72]	A failure to achieve an RER value of greater than 1.0 may be associated with pulmonary or cardiovascular disease, including deconditioning, or poor effort. It also may be related to the nutrient content of a meal eaten just prior to the CPX.

$P_{ET}CO_2$	$P_{ET}CO_2$ is the highest alveolar PCO_2 during the respiratory cycle. It is reflective of the heart's ability to deliver deoxygenated blood from the right side of the heart to the lungs. $P_{ET}CO_2$ also indicates physiological pulmonary dead space. That is, the mismatch between alveoli either un- or under-perfused or unventilated.	The normal range is from the upper 30s to mid/upper 40s in mmHg. A normal increase in $P_{ET}CO_2$ from rest to VT is 3-8 mmHg	A lower than normal value would be indicative of a reduced cardiac output or a ventilation-perfusion mismatch. $P_{ET}CO_2$ is correlated with cardiac output and is of prognostic utility in the assessment of patients with heart failure and pulmonary hypertension.[64, 73-75]
$\Delta VO_2/\Delta WR$	The slope of VO_2 as a function of work rate is a measure of efficiency. Smaller changes in VO_2 for equal changes in work rate indicate a greater efficiency (consumption of less oxygen for greater work), resulting in a smaller value of $\Delta VO_2/\Delta WR$.	In highly trained individuals the slope of $\Delta VO_2/\Delta WR$ is higher compared to a less-fit person. VO_2 typically increases linearly with increasing work rate. Above the anaerobic threshold the slope may be shallower owing to the decreased reliance on oxygen for the performance of work.	Changes to the $\Delta VO_2/\Delta WR$ slope can be the result of peripheral or central dysfunction. A drastic change in VO_2 is most often reflective of a change in cardiac output since it is the primary determinant of VO_2. Peripherally, oxygen extraction can also be compromised although acute changes are less common. See Figure 3.
VE/VCO_2	The VE/VCO_2 relationship reflects the ventilation required to expel a certain quantity of CO_2. This can be expressed as a ratio or a slope but the latter is preferred.	At sub-maximal exercise VE and VCO_2 closely mirror each other but the ratio does not increase much during sub-maximal exercise owing to the fact that ventilation easily keeps pace with metabolically created CO_2. At the ventilatory threshold CO_2 is produced in greater quantity and in normal subjects VE will increase non-linearly to keep pace.	The VE/VCO_2 slope has been demonstrated to be elevated in individuals with heart failure.[76-79] There is some evidence it may be abnormal in patients with exercise induced myocardial ischemia.[53]
VE/VO_2 or OUES	The VE/VO_2 relationship reflects the ventilation per quantity of oxygen consumed. OUES, the slope of the logarithmic regression curve expressing the relation between VO_2 and VE represents the rate of increase in VO_2 in response to a given VE. A steeper slope would be indicative of a greater uptake of oxygen in response to a given ventilatory rate.[80]	The normal range for the VE/VO_2 slope is 30-40. In highly trained individuals baseline VE/VO_2 is lower owing to greater efficiency, i.e. more oxygen being consumed with less ventilatory work. During exercise, VE/VO_2 decreases until the ventilatory threshold, when ventilation increases significantly in an effort to expire additional non-buffered CO_2.	Baseline OUES is elevated in patients.[81] OUES in patients is lower than in apparently healthy individuals. A review comparing the OUES to the VE/VCO_2 slope in the heart failure patient population revealed the superiority of the VE/VCO_2 slope in predicting adverse events.[82]

Test	Sens	Spec	PPV	NPV	Risks	Limitations
Cardiac Angiography/ Catheterization					-Death, MI, CVA: 0.2% - 0.3% -Minor complications (e.g. hematoma at catheter site): 1% - 2%[83] -Hemodynamic complications: 0.26%[84] -Risks related to radiation exposure -Dyes may be problematic due to allergies or co-morbidities	-Not a functional assessment; does not fully capture clinical significance of stenosis -Limited use in microvascular CAD -May not correlate well with function -Negative result is not definitive proof of absence of CAD[38]
CPX	87%[50]	74%	88%	72%	-Serious adverse events (MI or hospitalization): <1-5 per 10,000 tests -Death: 0.5 per 10,000 tests[85]	-If positive, further testing is needed to determine which vessels are involved
Ex ECG[31] **All** **Only women**	23-00% Compar- able	17-100% Lower	NR	NR	Same as above	-False positives are common and significant among women and those with baseline ECG abnormalities[16]
MPI[86] **Non-Ex** **Exercise**	72-93% 71-97%	28-100% 36-100%	NR	NR	-Risks related to exercise, same as above - Risks related to myocardial perfusion study include exposure to radioactive tracer	-Diagnostic accuracy impacted if > 85% HR target not achieved[87]
Ex Echo[88] **All** **+ Referral** **Bias**	71-97% 32-93%	41-100% 37-100%	71-100% 66-100%	40-93% 54-90%	-Risks related to exercise, same as above	-Diagnostic accuracy impacted if > 85% HR target not achieved[89] -Resting wall motion abnormalities make interpretation difficult[90] -Difficult to determine site of disease[33]

TABLE 4: SUMMARY OF DIAGNOSTIC ACCURACY. RISKS, LIMITATIONS OF COMMON TESTS TO DIAGNOSE CAD

	sens	spec	PPV	NPV		
MR[83] **CAD** **CABG patency**	50-94% 73-100%	42-100% 40-100%	NR	71-96%		-Spatial resolution is lower vs angiography and CT -Relative imaging time (vs MPI) is longer -Software and hardware may not be widely available -Metal medical devices are a contraindication -Claustrophobia -No data on improved outcomes
CT[83] **CAD**	30-100%	9-99%	NR	83-100%	-Radiation dose -IV administration of contrast medium can lead to allergic reaction or adverse events related to kidneys, especially in those with compromised renal function	-Relative imaging time (vs MPI) is longer -May be necessary to pharmacologically reduce HR -No data on improved outcomes

Abbreviations: Ex = exercise, sens = sensitivity, spec = specificity, PPV = positive predictive value, NPV = negative predictive value, NR = not reported, MR = magnetic resonance, CT = computed tomography, occl = occlusion, sten = stenosis, CAD = coronary artery disease, CABG = coronary artery bypass graft, CPX = cardiopulmonary exercise test

Table 5: Chronological Summary of Studies Using CPX in Suspected or Confirmed Myocardial Ischemia

| Author	Year	# of Subjects/Cardiac History	Gold Standard/Tests Compared	Significant Findings
Ehsani[40]	1984	27 asymptomatic patients (26 men) with CAD, all with prior MI	- EF determined by MUGA	- VO_{2max} was significantly lower in those whose EF decreased with exercise - Max O_2-pulse in subjects with decreased EF during exercise was lower vs those whose EF increased with exercise - ΔEF (exercise – rest), was significantly correlated with VO_{2max}, O_2-pulse - ΔEF, HR_{max} were the best predictors of VO_{2max} - VO_{2max} ~22% lower in patients with reduced EF during exercise
Koike[41]	1989	23 patients with heart disease (ischemic or valvular)	- None	- AT correlated with work rate at which LV dysfunction occurred
Koike[42]	1992	22 patients (19 men) with previous MI	- Cadmium telluride detector for EF	- VO_2/WR slope no different above and below AT - CO/WR slope significantly different (lower above the AT vs. above) - CO/VO_2 was also significantly different (lower above vs below AT)
Koike[43]	1994	-43 asymptomatic patients (36 men) with previous MI; 2 groups: - Group I: (n=20) EF > 35% - Group II: (n=20) EF < 35%	- Cadmium telluride detector for EF - Angiography to detect stenotic vessels	- Delayed time constant of VO_2 evident in patients with LV dysfunction (EF < 35%) - Time constant for CO was longer in patients with LV dysfunction - SV, HR increase impaired in subjects with EF <35%
Meyer[44]	1995	27 (all male) patients with CAD, 16 with previous MI; a second group of 10 patients with CAD received isosorbide dinitrate (ISDN)	- None	- AT preceded ST segment changes indicative of ischemia and was associated with a lower WR, RPP, VO_2, lactate, HR in the 2nd group of patients, after ISDN administration, the onset of ischemia occurred at a greater workload, VO_2 and lactate level; no changes to AT

Ajisaka[53]	1996	- 22 patients (17 men) with CAD performed CPX before and after PTCA	- EF determined by echocardiography - stenosis determined by angiography	- Significant differences between subjects with s - Successful PTCA vs failed PTCA - VE/VCO_2 slope, peak VO_2 and VO_2 at VT improved in successful PTCA group; worsened in failed PTCA group
Klainman[45]	1996	- 58 patients with suspected CAD; 3 Groups: - Group I: no ST segment changes/no angina - Group II: ST segment changes only (silent) - Group III: ST segment changes and angina	- EF determined by MUGA - Angiography performed only in symptomatic or silent groups	- O_2-pulse higher in patients with ST segment changes but no angina vs ST segment changes with angina - EF declined during exercise in the symptomatic group and increased only slightly in the silent ischemia group - No significance difference in # of vessels affected between silent and symptomatic groups
Lele[46]	1996	- 20 patients (15 male) with CAD compared to 10 healthy controls (8 males)	- EF and diastolic function by MUGA - MPI to detect reversible perfusion defects - CAD confirmed by angiography prior to CPX	- Significant negative correlation between diastolic function during exercise (time to peak filling) and VO_{2max}
Hsi[91]	1997	- 43 post MI patients - 43 trained men - 44 untrained men	- EF determined by MUGA	- Low O_2-pulse/body weight significantly associated with LV dysfunction and ischemia during exercise
Klainman[54]	1998	- 29 patients (36 males) with CAD performed CPX before and after PTCA	- Coronary angiography for determination of stenotic vessels before CPX	- All patients with successful PTCA had improvements in VO_{2max}, O_2-$pulse_{max}$, O_2-pulse curve score, AT
Zafrir[47]	1999	50 patients (49 men) classified as having </> 20% ischemia	- MPI for % ischemia determination	- VO_2 and extent of myocardial ischemia were significantly negatively correlated - More ischemia (vs. less) associated with significantly lower $\Delta VO_2/\Delta WR$, VT - VT was the most sensitive predictor of % ischemia

Adachi[55]	2000	17 male patients with CAD all of whom had PTCA	- Coronary angiography for stenotic vessels	- Time constant of VO_2 uptake shorter after PTCA, except in those who had a failed PTCA - Absolute VO_2 values were no different before vs after PTCA in either successful or failed PTCA patients
Belardinelli[59]	2001	38 patients (31 males) with CAD and LV dysfunction; 2 groups, one receiving trimetazidine and the other a placebo	- Echocardiography for EF, diastolic function, systolic wall thickening, LV wall motion	- VO_{2peak} improved in treatment group with no significant changes in hemodynamic variables - Contractile improvement demonstrated in the treatment group correlated with improvements in VO_{2peak}
Bigi[48]	2001	46 patients (39 males) with anterior myocardial infarction and LV dysfunction	- Coronary angiography to determine stenotic vessels - EF determined by MUGA - ECG for determination of myocardial ischemia (based on ST segment change)	- CO_{AT} in those with ECG changes lower than in those without - CO_{AT} value of 7.3 L/min was the best cutoff value for identifying those with multi-vessel CAD - ECG Sensitivity, Specificity, NPV, PPV: 64%, 43%, 57%, 50%, respectively - CO_{AT} Sensitivity, Specificity, NPV, PPV: 72%, 62%, 69%, 65%, respectively - $CO_{AT} < 7.3$ L/min was predictive of future events and event-free survival
Klainman[92]	2002	46 patients (39 males) with ischemic heart disease classified into 4 groups based on resting EF, ΔEF with exercise, ECG changes indicative of diastolic dysfunction	- EF determined by MUGA -	- Significant negative correlation between LV function and O_2-pulse score (points system to classify behavior – normal, low, flat and low, declining)
Belardinelli[50]	2003	202 patients (173 men) with CAD	- MPI used as gold standard for ischemia detection	- O_2 pulse flattening duration and $\Delta VO_2/\Delta WR$ slope were predictive of ischemia - inclusion of O_2-pulse flattening duration and $\Delta VO_2/\Delta WR$ slope improved the sensitivity and specificity of ECG from 46% to 87% and 66% to 74%, respectively

Castro[61]	2004	15 patients (12 males) with CAD with exercise-induced myocardial ischemia underwent CPX before and after taking pyridostigmine or placebo, a cholinesterase inhibitor	- None	- VO_{2peak}, VCO_2, VE, O_2-pulse were all improved after pyrostigmine administration vs. placebo and delaying the onset of exercise induced myocardial ischemia and indicating the sensitivity of these variables to the consequences of ischemia
Bussotti[51]	2006	48 patients with (n=35) and without (n=13) significant coronary lesions; all had asymptomatic ST segment changes indicative of ischemia	- Coronary angiography for determination of stenotic vessels	- % predicted VO_{2peak} was significantly lower in those with significant coronary stenosis - $\Delta VO_2/\Delta WR$ slope was less steep in those with significant lesions vs those without
Contini[57]	2006	Single subject case study	- Cardiac CT angiography confirmed stenosis	- Following PTCA O_2-pulse, $\Delta VO_2/\Delta WR$ and VO_2 normalized
Munhoz[52]	2007	87 patients with suspected or confirmed CAD	- MPI used as a gold standard to detect ischemia	- No difference in CPX variables between patients presenting with vs without ischemia - Peak O_2-pulse lower in subjects with extensive vs mild ischemia
Tiano[62]	2007	38 patients (33 males) with CAD divided into two groups, one of which received Coenzyme Q10 (CoQ_{10}) supplementation, the other did not	- None	- CoQ_{10} supplementation resulted in significant improvements in VO_{2peak}, VO_{2AT}, VE, O_2-pulse$_{peak}$, $\Delta VO_2/\Delta WR$, WR_{peak}, SBP_{peak} confirming the sensitivity of these variables to changes in LV function
Belardinelli[60]	2008	116 patients (97 males) with ischemic heart disease, LV dysfunction; 4 groups were compared: I) trimetazidine + exercise II) exercise + placebo III) trimetazidine IV) Placebo + untrained	- Echocardiography to detect diastolic and systolic function, and EF	- Trimetazidine plus exercise resulted in the greatest gains in VO_2, LV EF vs trimetazidine or exercise alone confirming the sensitivity of VO_2 to improvements in LV function

Chaudhry[58]	2008	Single subject (male) case study	- Coronary angiography to detect stenotic vessels	- No ST segment changes indicative of ischemia - O_2-pulse gradually decreased with increasing work rate, abrupt decrease in the slope of VO_2/WR and an increase in the slope of $HR-VO_2$
Inbar[56]	2008	14 subjects (13 males) had cardiac catheterization; 8 went on to have PTCA, the other 6 did not; all underwent CPX	- The ability of CPX to detect myocardial ischemia was compared to ECG	- Pre-PTCA ECG specificity, sensitivity: 100%, 25%, respectively - Post-PTCA ECG specificity, sensitivity: 20%, 64%, respectively - Those with PTCA had significant improvements in VO_{2peak}, VAT, O_2-pulsepeak, and O_2-pulse score vs those who did not undergo PTCA - CPX improved ECG sensitivity and specificity by 89% and 12%, respectively

FIGURE 1: OVERVIEW OF INSTRUMENTATION USED FOR CARDIOPULMONARY EXERCISE TESTING
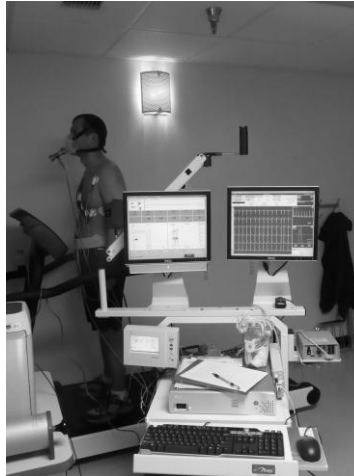
Legend for Figure 1

- Metabolic Cart: The subject breathes through a mouthpiece (with nose sealed off by a clip) or facemask. Non-rebreathing valves are used to separate inspired and expired air. Oxygen and carbon dioxide gas analyzers and sensors measure air flow over time and are used for volume measurements. Finally, ventilation, O_2 consumption and CO_2 production (all in L/min) are calculated via breath-by-breath techniques. Continuous ECG monitoring and periodic recording of HR and BP are also standard and automated on most modern systems.[93]
- Mode: Treadmill or Bicycle
- Workload Determination/Protocol: Ideally, the functional capabilities of the subject determine the protocol used however in clinical practice the most often used is the Bruce Protocol.
- Personnel: American Heart Association guidelines state clinicians present to supervise the test should have demonstrated competence in the area of exercise testing. Those present should include at a minimum include a physician, nurse, exercise physiologist and/or physical therapist.[85]
- Communication: Verbal communication is limited due to the facemask or mouthpiece and therefore prior to the test it is important to establish the use of hand signals or written signs that can be pointed to.
- Variables/Measures: See Table 3 for full listing
- Indications/Contraindications: See Tables 1 and 2 for full listing

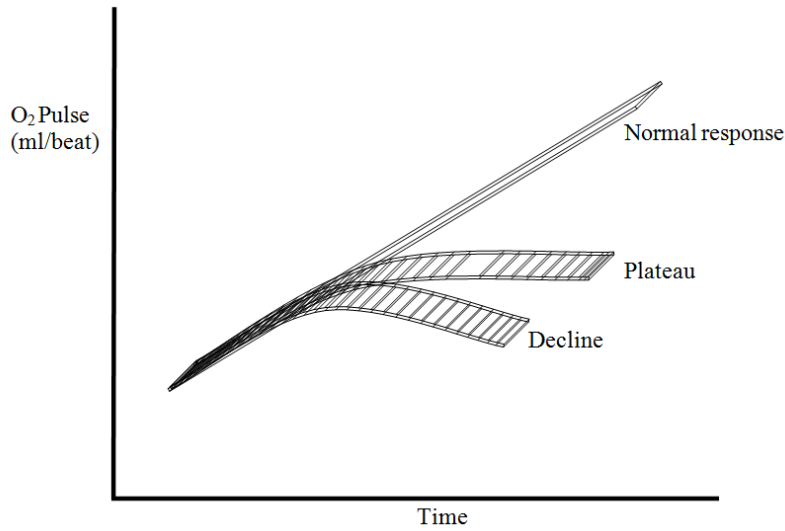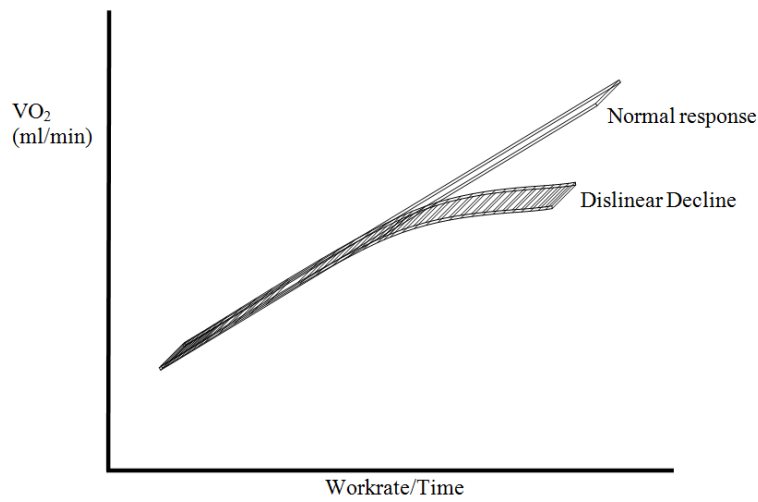**FIGURE 2: NORMAL AND ABNORMAL OXYGEN PULSE RESPONSE DURING PROGRESSIVE EXERCISE TESTING**

FIGURE 3: NORMAL AND ABNORMAL CHANGE IN OXYGEN CONSUMPTION/CHANGE IN WORKRATE RESPONSE DURING PROGRESSIVE EXERCISE TESTING

Chapter 2: Real-Time Decrease in the Oxygen Uptake Efficiency Slope Identifies Myocardial Perfusion Defects in Men Undergoing Ischemic Evaluation

ABSTRACT

Introduction: Cardiopulmonary exercise test (CPX) variables may aid in the diagnosis of coronary artery disease (CAD). Specifically, an abnormal flattening or declining trajectory of the oxygen (O_2) pulse has been shown to be predictive of the onset of myocardial ischemia in patients previously diagnosed with CAD. However, a more heterogeneous clinical population without prior work-up bias has not been studied. Moreover, additional CPX variables have not been assessed. The purpose of the current investigation is to address these gaps in the literature.

Methods: Three hundred and three subjects with symptoms suggestive of myocardial ischemia underwent CPX and single photon emission computed tomography (SPECT) myocardial perfusion study (MPS). Ventilatory efficiency was calculated by the oxygen uptake efficiency slope (OUES). The change in the OUES was calculated by subtracting the value of OUES during the last 25% (OUES75) of exercise from the OUES obtained during the first 50% (OUES50). O_2 pulse flattening duration was calculated by subtracting the total exercise time from the time at which the peak O_2 pulse occurred.

Results: A negative change in OUES was predictive of a positive MPS (area under receiver operating characteristic curve [AUC] = 0.59, 95% CI [0.52, 0.65], $p = 0.02$), and even more strongly so in those with a more a definitive (i.e. not equivocal) perfusion defect (AUC = 0.67, 95% CI [0.57, 0.77], $p < 0.01$). A gender specific analysis revealed the diagnostic significance of the OUES was isolated to male subjects for both any level of positive MPS (AUC = 0.67 95% CI [0.59, 0.76], $p < 0.001$) and more so in those with a more definitive perfusion defect (AUC = 0.76

95% CI [0.67, 0.85], p <0.001). The predictive ability of O_2 pulse could not be confirmed in the whole cohort; however, in males the change in O_2 pulse from rest to peak was predictive of a mild-severe perfusion defect (AUC = 0.66, 95% CI [0.52, 0.80], p = 0.02).

Conclusions: This is the first time that real-time change in ventilatory efficiency, assessed by the OUES, has been shown to be predictive of positive MPS and possible CAD. Changes in the OUES only seem to provide diagnostic value in males when MPS is used as the gold-standard assessment.

Introduction

Coronary artery disease (CAD) accounts for more than half of all cardiovascular events suffered by men and women under the age of 75 in the United States. An estimated 7 million inpatient cardiovascular operations and procedures are performed each year. As a result, the diagnosis of CAD will have an estimated cost of $177.1 billion in 2010.[94] The proliferation of diagnostic tests to detect CAD continues to expand, keeping pace with technological advances. Even so, the use of the traditional exercise test remains central to the assessment of patients with suspected CAD. An area that has received relatively little clinical attention is the diagnostic utility of ventilatory gas analysis during the traditional exercise test. Given the coupling of the cardiovascular and pulmonary systems during physical exertion, real-time abnormal alterations in ventilatory expired variables may be valuable in the diagnosis of CAD. Research over the past 20 years has supported this premise.[95]

Currently, cardiopulmonary exercise testing (CPX), the term used to describe the integration of ventilatory expired gas analysis and the traditional exercise test, is used to measure aerobic capacity directly, differentiate between cardiac and pulmonary causes of exertional dyspnea, assess prognosis in patients with heart failure[96] and, more recently, to diagnose and gauge disease severity in pulmonary hypertension.[97] The rationale supporting the use of CPX in diagnosing CAD lies in its ability to detect real-time, abnormal alterations in ventilatory expired gas that may be reflective of the onset of ischemia-induced left ventricular (LV) dysfunction.

Several CPX-derived variables have been identified as being indicators of LV dysfunction precipitated by myocardial ischemia.[95] The oxygen (O_2) pulse [oxygen consumption/heart rate (VO_2/HR)], which follows a linear trajectory during a progressive exercise test, has been shown to abnormally flatten or decline in the presence of exercise induced

myocardial ischemia (EIMI).[50] Similarly, the normally linear relationship between VO_2 and work rate (WR), has been demonstrated to prematurely flatten in the presence of EIMI.[50] Strengthening these cross-sectional observations are studies demonstrating an improvement in O_2 pulse and the VO_2-WR slope following successful percutaneous coronary intervention (PCI).[60, 62]

Two recent investigations have focused on the ability of CPX variables to detect EIMI.[50, 52] Belardinelli et al.[50] prospectively studied 202 patients (86% male) with confirmed CAD and compared the results of CPX and the traditional exercise test variables, using a lower extremity (LE) ergometer as the mode of exercise, to myocardial perfusion studies. By logistic regression, the independent predictors of a reversible perfusion defect were duration of O_2 pulse flattening (measured as the time between the occurrence of maximum O_2 pulse and total exercise time) and flattening of the VO_2-WR slope. When both of these CPX variables were positive, the sensitivity and specificity of the exercise test (i.e. ST segment changes) were improved by 89% (from 46% to 87%) and 32% (from 66% to 74%), respectively. Munhoz et al.[52] assessed the ability of O_2 pulse to identify an abnormal myocardial perfusion study. This was the first study which employed a treadmill instead of a LE ergometer. This is clinically relevant given the former is the primary exercise mode utilized in exercise testing labs in the United States. Of the 87 patients (71% male) included in this analysis, 16 had a prior myocardial infarction, 49 had prior cardiac catheterization, 30 had undergone PCI and nine had coronary artery bypass surgery. All subjects underwent CPX followed by a myocardial perfusion study and were divided into two groups based on the presence or absence of ischemia. Oxygen pulse at rest, 25%, 50%, 75% and peak VO_2 was not different between the two groups. However, in a separate comparison in which the ischemia group was divided into mild vs. extensive ischemia, O_2 pulse at peak VO_2 was significantly lower in the latter.

While these initial investigations are promising, additional research is needed to more clearly elucidate the value of CPX in the evaluation of those with suspected CAD. Of the numerous questions that have not been answered, first, it remains to be determined if CPX will remain diagnostically accurate in an "all-comers" patient population. To this point, research has included subjects who were either exclusively or predominantly diagnosed with CAD at study enrollment, introducing work-up bias as a potential confounding factor. Several large studies confirm that in today's clinical environment, the patient population referred for exercise testing is more heterogeneous, with the majority being low risk, presenting with signs and/or symptoms merely suggestive of CAD.[98, 99] This illustrates the importance of the use of relatively inexpensive diagnostic tests to better identify those who require additional, often more costly, procedures.

In addition, a comprehensive assessment of all potentially valuable CPX variables, beyond O_2 pulse and VO_2-WR slope, in the diagnosis of EIMI has not been performed. For example, real-time abnormal changes in the trajectory of ventilatory efficiency may prove valuable. The most common expressions of ventilatory efficiency are the minute ventilation/carbon dioxide (VE/VCO_2) slope and the oxygen uptake efficiency slope (OUES). Both variables reflect the integrated function of the cardiac and pulmonary systems during physical exertion and are thus potentially valuable in the detection of the onset of ischemia-induced LV dysfunction. Moreover, variables reflecting ventilatory efficiency may have diagnostic advantages over the O_2 pulse and VO_2-WR slope. For example, these variables may be less affected by the influence of treadmill hand rail use and pharmacologically-induced alterations in heart rate. Of the two common measures of ventilatory efficiency, the OUES holds particular promise given a normal response during progressive exercise follows a tight linear

trajectory. Thus, even subtle negative deviations in this response may prove to be significant in detecting ischemia-induced LV dysfunction. Given these gaps in the literature, the objectives of the present study are to: 1) assess the diagnostic value of CPX in a group of subjects undergoing clinical assessment for CAD without prior work-up bias and 2) more comprehensively assess the utility of all relevant CPX variables in identifying reversible myocardial perfusion defects quantified by nuclear imaging.

Methods

The current investigation prospectively assessed 303 patients who presented to the Non-Invasive Stress Laboratory of Virginia Commonwealth University Medical Center from May 2009 to February 2010. Subjects presented with symptoms suggestive of myocardial ischemia and/or a previous history of CAD. Common indications included chest pain (65.3%), dyspnea (8%), history of CAD (5%), syncope (1.3%), palpitations (3%) and/or abnormal ECG (2.4%). Exclusion criteria were myocardial infarction or PCI within three months of testing, previous diagnosis of congestive heart failure, known left ventricular ejection fraction <35%, evidence of moderate lung disease by pulmonary function test, moderate or severe aortic or mitral valve stenosis, unstable angina or uncontrolled hypertension, previous pacemaker implant or coronary artery bypass grafting, orthopedic/neurologic conditions that limited exercise performance, and/or inability to collect interpretable ECG and nuclear imaging data. The traditional cardiac risk factors, hypertension, lipid profile, tobacco use, family history of early coronary disease, physical activity and diabetes, were recorded. Physical activity frequency, duration and intensity were measured by patient self-report. Exercise tests were performed in the fasting state and patients were instructed to avoid all caffeine-containing food or drink in the 4 hours prior to

the test. Patients were instructed to follow the recommendation of their physician on taking

prescribed medications. However, it was noted if the patient was taking a beta-blocker and if so,

whether it was taken as prescribed on the day of the test.

The protocol was approved by the Institutional Review Board at Virginia Commonwealth

University. All subjects signed an informed consent prior to inclusion in the study.

Nuclear Myocardial Perfusion Imaging Procedures

All subjects had the stress portion of a single photon emission computed tomography

(SPECT) myocardial perfusion study (MPS) the same day as the standard exercise test with

ventilatory expired gas analysis. However, based on referral source and/or patient

characteristics, some subjects underwent the rest portion of the MPS on a different day. Two

main referral sources exist for this clinic. The first is the Emergency Department (ED) from

which patients are referred for follow up stress MPS after undergoing an evaluation for possible

myocardial ischemia or infarction. At the time of the ED visit patients undergo rest SPECT

MPS. Nearly half (48.8%) of the subjects included in the present investigation were referred

through the ED. The second referral source is primary care and cardiology physicians. These

patients typically have both the rest and stress portions of the study done on the same day. The

remaining 51.2% of the subjects in this study were referred in this manner.   Given this, various

SPECT MPS protocols were utilized depending on patient characteristics and nuclear isotope

availability. During the data collection period there was a worldwide shortage of one of the

commonly used nuclear isotopes, technetium 99 (aka tetrofosmin). As a substitute, thallium-201

(TL-201) was used. It has been shown that TL-201 and tetrofosmin are similar in detecting

CAD.[100] All SPECT MPS were done with ECG gating (16 time frames in the heart cycle) to

allow for determination of global and segmental left ventricular function as well as for detection of perfusion abnormalities. Forty percent of the tests were done with technetium and in the remainder thallium was used.

Each result was categorized as the presence and extent of reversibility according to the following: 0/normal = no evidence of attenuation or reversibility or fixed defect likely due to soft tissue attenuation; 1/equivocal = small size and low grade reversible defect; 2/mildly abnormal = small size and moderate grade or moderate size and low grade reversible defect; 3/moderately abnormal = moderate size and moderate grade reversible defect; 4/severely abnormal = moderate size and high grade or large size and high grade reversible defect.

Standard Exercise Test Procedures

All exercise tests were done on a motorized treadmill (GE Healthcare Series 2000, Waukesha, WI) using the Bruce Protocol.[101] Exercise testing procedures outlined by the American Heart Association were followed for all assessments.[3, 102] All patients were continuously monitored by a 12-lead ECG (GE Marquette 12SL, Waukesha, WI) and hemodynamic measurements were made during each stage of the protocol. Blood pressure was measured with an automated sphygmomanometer (SunTech Tango+, Morrisville, NC) with auditory confirmation. Patients were encouraged to exercise to their maximum tolerance. Maximum heart rate (MHR) was defined as heart rate at peak exercise. Age-predicted maximum heart rate (APMHR) was calculated with the following: APMHR = 220 − age. Percent-predicted maximum heart rate (PPMHR) was calculated with the following: (MHR/APMHR)*100. Maximum systolic blood pressure (SBP) and diastolic blood pressure (DBP) were defined as SBP and DBP at peak exercise. The following exercise test termination criteria were used:

onset of severe typical angina, arrhythmias (frequent premature ventricular contractions; greater than or equal to 3 beats of non sustained ventricular tachycardia; new onset atrial fibrillation, atrial flutter or atrial tachycardia with rapid response; second or third degree heart block), hypotension, bradycardia or decrease in heart rate with same or greater workload, dyspnea, intermittent claudication, central nervous system symptoms, marked hypertension, greater than 2 mm of horizontal or down sloping ST segment depression or ST elevation $\geq$ 1 mm, and patient's request to stop or inability to keep up with the treadmill.

Dyspnea and angina were measured using 4 point scales.[102] For level of exertion, the 6-20 Borg Rating of Perceived Exertion (RPE) scale was used.[103]

Cardiopulmonary Exercise Test Procedures

Ventilatory expired gas was collected for each test using a metabolic cart (Vmax Encore, SensorMedics, Yorba Linda, CA). Before each test, the equipment was calibrated in standard fashion using reference gases and a 3-liter syringe. Ventilatory expired gas analysis data collection began at rest and continued throughout the duration of the test. The first minute was used to familiarize the subject to the equipment, to normalize ventilatory pattern and to allow for collection of baseline data.

Minute ventilation (VE), oxygen consumption (VO_2), and carbon dioxide production (VCO_2) were acquired breath-by-breath, and averaged over 10-second intervals. Peak VO_2 is expressed as the highest 30-second averaged sample obtained during the exercise test in $mLO_2 \cdot kg^{-1} \cdot min^{-1}$. Peak respiratory exchange ratio (RER) is expressed as the highest averaged sample obtained during the exercise test. For the oxygen uptake efficiency slope (OUES), VE, averaged over 10 second intervals, was transformed into its logarithmic equivalent. The OUES

was determined via least squares linear regression (VO_2 = a $log_{10}VE$ + b; VO_2 and VE are expressed in L/min) by spreadsheet software (Microsoft Excel, Microsoft Corp., Bellevue, WA).[80] All exercise data were used to calculate the OUES. Change in OUES (OUES50-75) was calculated by determining the difference between the value of OUES from the first half of the exercise bout (OUES50) and the last 25% of the exercise bout (OUES75). VE and VCO_2 values, acquired from the initiation of exercise to peak, were entered into spreadsheet software (Microsoft Excel, Microsoft Corp., Bellevue, WA) to calculate the VE/VCO_2 slope via least squares linear regression (y = mx + b, m=slope). A change in VE/VCO_2 slope (VE/$VCO_2$50-75) was assessed in the same manner as described for OUES. The O_2 pulse was calculated in 30 second intervals by dividing VO_2 by heart rate at rest and throughout exercise. Peak O_2 pulse was the highest 30-second averaged value during the exercise bout. Oxygen pulse flattening duration, initially described by Belardinelli et al[50], was calculated as total exercise time minus time at which peak O_2 pulse occurred. Change in O_2 pulse was calculated as the difference between the highest O_2 pulse during exercise and the resting value.

Statistical Analysis

Statistical analysis was performed using SPSS 17.0 (SPSS Inc, Chicago, IL). Unpaired student's t-test was used to compare continuous variables of interest between subjects. One way ANOVA was used to compare clinical, hemodynamic and metabolic interval data among groups of subjects stratified according to the three levels of MPS result (negative, equivocal, and mild – severe). The Kruskal-Wallis test compared differences in ordinal data (i.e. RPE, dyspnea, angina scales), while chi-square analysis assessed differences in nominal data (i.e sex, race) amongst the three groups. Receiver operator characteristic (ROC) curve analysis was used to

assess the predictive ability of key ECG stress test and CPX variables. When an area under the curve (AUC) was found to be significant and an optimal threshold value was identified, a two-by-two contingency table was constructed to determine the relative risk ratio and 95% confidence interval of that given threshold. Due to the known impact of beta-blocking agents on the heart rate response[104] during exercise, a subgroup analysis was performed on the diagnostic utility of key variables in subjects who were not prescribed a beta-blocking agent. Lastly, the ability of standard exercise test and ventilatory expired gas variables to identify subjects with a reversible myocardial perfusion defect was separately performed in males and females. All statistical tests with a p-value <0.05 were considered significant. All means are expressed ± standard deviation.

Results

Three hundred and three subjects (157 males, 146 women) successfully completed all assessment procedures. Mean age and BMI were 49.9 ±11.6 years and 30.4 ±6.5 kg/m^2, respectively. The majority of subjects (86.1%) had no history of heart disease. Of these, 8.3% had undergone cardiac catheterization without intervention. Ten percent of subjects had a history of CAD: 8.9% percent had a previous PCI, and 1.1% had a myocardial infarction (MI) without intervention. Electrical abnormalities and mild valvular disorders were present in 3.9% of the subjects. The majority (73.6%) were taking prescribed medications on the day of the test. Of these, slightly more than half (55.0%) were taking an anti-hypertensive, 31.4% were taking a lipid-lowering agent, 28.1% were taking aspirin and 11.2% were taking a medication for diabetic management. More than half (57.4%) reported no regular physical activity. Another 27.7%

reported exercising less than 3 days per week and only 14.8% reported participation in exercise

on 4 days or more per week. The mean number of cardiovascular risk factors was 3.0 ± 1.5.

Resting heart rate was not different between males and females (72.2 ± 15.0 vs. 74.8

± 14.1, respectively; $p = 0.11$) however, resting blood pressure was significantly higher in males

vs. females ($137.3 \pm 21.4/84.1 \pm 13.1$ vs $130.8 \pm 18.6/80.7 \pm 9.4$ mmHg, respectively; $p < 0.05$).

Resting O_2 pulse was higher in males vs. females (15.7 ± 4.7 vs. 14.6 ± 3.2 mL/beat, $p < 0.05$).

Two hundred and two subjects (66.7%) had a normal myocardial perfusion study, 69

subjects (22.8%) had an equivocal study and 32 (10.5%) had a mildly, moderately or severely

abnormal stress MPS. Of those with an abnormal result, the percent of myocardium involved

ranged from 1-14%, with a mean of $4.39 \pm 3.31\%$. The majority of the defects were small in size

(72.5%) and low in grade (84.2%). Wall motion abnormalities were present in 7.6% of those

with an abnormal stress MPS. The frequency of negative, equivocal and positive MPS was

different among men and women (93, 42, 22 vs. 109, 27, 10, respectively; $p < 0.01$).

There was no difference in age between each of the MPS groups (Table 1). Males

formed a higher percentage of patients in the mild – severe group and the equivocal MPS group

than in the negative group. Patients with a mild – severe defect had a significantly higher BMI

than the negative group and more risk factors than either the equivocal or negative groups.

Patients in the mild – severe group were more likely to have typical chest pain or shortness of

breath than those in the equivocal or negative group. Treadmill time was significantly less in the

mild – severe group compared to the negative perfusion group and was significantly less in the

equivocal group than the mild–severe group. Finally, OUES50-75 was significantly different in

the mild–severe perfusion defect group than in the negative group.

Of the 303 subjects, 285 (94.1%) completed the protocol with no ST segment changes indicative of ischemia. Nine subjects (3%) had at least 1 mm, eight subjects (2.6%) had at least 2 mm, and two subjects (0.7%) had at least 3 mm of ST segment depression in at least one lead. Standard ECG stress testing was unable to identify subjects with a positive MPS (including equivocal tests or when only mild–severe perfusion defects were considered). (Table 2)

The duration of O_2 pulse flattening was not able to identify subjects with a positive MPS. This finding was consistent regardless of degree of perfusion defect, beta-blockade status, or gender. OUES50-75 produced a statistically significant diagnostic model which remained so regardless of beta blockade status. It was more strongly predictive of a positive MPS among those with mild–severe ischemia. A change in VE/VCO$_2$ slope (VE/VCO$_2$50-75) was found not to be diagnostically significant for MPS result. (Table 2)

When considering males alone, the ability of OUES50-75 to identify a positive MPS increased, especially in those with mild–severe perfusion defects (table 2). Additionally, a change in O_2 pulse from rest to peak was predictive of mild–severe ischemia in males only. None of the diagnostic models were statistically significant in the female subgroup (Table 2).

In the male group, optimal diagnostic thresholds for O_2 pulse$_{peak-rest}$ and OUES 50-75 were 10 ml/beat and 0, respectively. Male subjects with an OUES < 0 (i.e any amount of decline in slope) were 2.0 times more likely (95% CI [1.4, 3.0], p< 0.001) to have any degree of perfusion defect and 5.4 times more likely (95% CI [2.1, 13.8], p< 0.001) to have a mild–severe perfusion defect. Figure 2 illustrates two cases from the present investigation; one in which the OUES remains generally linear while the other depicts a substantial decline at the terminal portion of exercise. The former had a negative MPS while the latter had a moderate perfusion defect. Male subjects with an O_2 pulse$_{peak-rest}$ < 10 were 3.6 times more likely (95% CI [1.7, 7.8],

p<0.05) to have a perfusion defect that was mild–severe. Relative risk ratios for the OUES 50-75 are illustrated in Figure 1.

Discussion

To our knowledge, the present study is currently the largest prospective analysis on the use of ventilatory expired gas in conjunction with traditional exercise testing procedures to aid in the non-invasive diagnosis of CAD. Importantly, this is the first study to include a majority of patients without a prior diagnosis of CAD, providing a better reflection of the type of patient being referred for this type of assessment in the current clinical environment. Moreover, a significantly greater percentage of females were included compared to similar previous investigations.[95]

The OUES finding is novel. Baba et al[105] first described the OUES in 1996 in a study assessing cardiovascular function in a group of children with congenital heart disease. OUES is a single point item that reflects both cardiovascular and pulmonary function.   Previous research has shown the OUES to be strongly linear throughout a progressive exercise test[106-108]. It is the strong linearity of the OUES that makes real-time deviations particularly attractive as a potential diagnostic tool. Under the condition of left ventricular dysfunction secondary to myocardial ischemia, an abnormal decline in OUES may be posited and the present investigation demonstrates that such a response at the terminal portion of exercise is in fact reflective of an abnormal MPS in male subjects.

Previous investigations have focused primarily on the ability of OUES to act as a surrogate for peak VO_2, one that is independent of effort and stable across the exercise duration. It has been repeatedly shown to be highly correlated with peak VO_2 and the VE/VCO_2 slope in

patients with heart failure and those with confirmed CAD.[109-111] Although it cannot predict peak VO_2[111] it has been shown to classify subjects with intermediate peak VO_2 values into clinically important categories and is sensitive to aerobic exercise training.[81] It has also been shown that OUES is significantly higher in subjects following PCI with or without history of myocardial infarction compared to subjects undergoing coronary artery bypass surgery with or without myocardial infarction. This suggests that OUES is sensitive to disease severity. The use of real-time change in the OUES to indicate the likelihood of an abnormal MPS has not previously been reported. However, one previous investigation by Arena et al.[106] found a real-time decline in the OUES was correlated with increasing aortic stiffness in apparently healthy subjects. This previous investigation supports the hypothesis that real-time change in the OUES is reflective of cardiovascular health and function.

Analysis of the real-time trajectory of O_2 pulse behavior (i.e. flattening time) in this study was not predictive of an abnormal MPS. However in males O_2 pulse$_{peak-rest}$ emerged as a predictor of ischemia. This result both validates and refutes previous findings. It is important to note that in most of the studies to-date, in contrast to our study, the majority of the subjects were male. For example, in the Belardinelli and Munhoz studies, men represented 86% and 71% of the participants, respectively.[50, 52] In contrast, in the present study nearly 50% of the subjects were female. Interestingly, we found that a change in O_2 pulse (O_2 pulse$_{peak}$ −O_2 pulse$_{rest}$) was predictive of a mild–severe perfusion defects only in males. This result seems to validate the findings of Munhoz et al. who showed that peak O_2 pulse was significantly different in those with mild vs. moderate or severe ischemia.[52] However, O_2 flattening duration, as Belardinelli assessed it[50], was not predictive of abnormal MPS.

There are a number of potential explanations for the lack of predictive ability of O_2 pulse in the whole cohort. First, previous studies included only patients with an established diagnosis of CAD, who likely had lower resting ejection fraction and were older, likely leading to worse baseline and exercise myocardial function. Moreover, only a small percentage (approximately 10%) of the subjects in this study had definite evidence of ischemia which was largely mild. In contrast, in the Belardinelli cohort,[50] most (70%) had evidence of moderate-severe ischemia. Ultimately, in the relatively younger and healthier cohort included in the present analysis, there may exist a greater ability to adapt to small declines in LV function. In other words, O_2 pulse may lack the necessary resolution to detect small changes. Conversely, the OUES response to progressive exercise is tightly linear under normal physiologic conditions as has been shown in a group of patients with stable CAD.[112] Thus, even the onset of low level LV dysfunction at the terminal portion of exercise may be reflected by a decline in the OUES.

As was previously noted, neither VE/VCO_2 slope using 100% of the exercise data, nor the change in slope was diagnostic for a positive MPS of any level. VE/VCO_2 slope has been shown to be of particular value in the heart failure patient population where an abnormally elevated slope (i.e. ≥ 34) has been shown to be highly prognostic for future morbidity and mortality from cardiovascular events. In the current cohort, the mean VE/VCO_2 slope was 22.2 ± 3.3, well within the range of what would be considered a normal response. Given this low variability amongst the response, it may be there was low diagnostic resolution to detect small changes. Moreover, the production of CO_2 is highly variable given individual metabolic attributes and fitness level and while the VE-VCO_2 relationship is generally linear, there is more variability compared to the OUES. This increased variability in the linear presentation of the VE/VCO_2 slope may have also contributed to the lack of diagnostic ability of this variable.

The findings of the present study relating to diagnostic disparity according to gender may be at least partially explained by baseline differences. The males in this study had significantly lower ejection fractions, lower maximal HR, and higher peak systolic blood pressure. This may reflect a greater pre-test likelihood for having a positive test since these variables have been associated with worse overall function. However, a more compelling explanation may be related to the differing presentation of ischemic heart disease in men and women. First, women with complaints of chest pain are much less likely to have anatomically significant coronary artery stenosis (defined as > 50% lesion) than men with similar complaints.[113] Despite this, women have greater rates of myocardial ischemia, worse prognosis and consume greater health care dollars in an attempt to diagnose and treat ischemic heart disease.[114] In a recent review, Shaw et al.[115] summarized previous research indicating the various etiologies of ischemic heart disease in women to include abnormal coronary activity, microvascular dysfunction, subendocardial ischemia and plaque erosion/distal microembolization. This difference in presentation may impact the accuracy of commonly used tests.[116] For example, SPECT MPS performed with thallium results in lower specificity and sensitivity to detect myocardial ischemia in women. Echocardiography and the use of ECG gating during SPECT MPS, which allow the quantification of ejection fraction and the visualization of wall motion abnormalities, result in greater accuracy.[117] In addition, the adoption of technetium as the nuclear isotope of choice appears to mitigate this problem. Although the present investigation did not elucidate a predictive model for the detection of a positive MPS it is possible that the differences relate to the gold standard used and not the CPX itself. Emerging techniques may provide a solution to this gender-related difference in diagnostic accuracy and supports future analyses into the value of exercise testing with ventilatory expired gas analysis in female cohorts. Cardiac magnetic

resonance imaging (cMRI) may be better at detecting the underlying pathology of ischemic heart disease in females by determining blood flow through coronary arteries and evaluating myocardial metabolism.[118, 119] One small study found subendocardial hypoperfusion, largely undetectable by today's clinical standards, in a group of mostly female patients with angina, exercise-induced ST segment changes but non-obstructive CAD (i.e Syndrome X).[120] Therefore assessment of the diagnostic potential of an abnormal OUES change, in females with suspected myocardial ischemia, while using cMRI as the gold standard seems to be a viable direction for future investigations.

A limitation of this study is the lack of cardiac catheterization data to confirm the MPS results. The majority of patients had normal or relatively mild perfusion defects and a low risk profile, so angiography would not be clinically indicated. However, previous research has demonstrated a positive MPS is a significant predictor of adverse events regardless of catheterization findings.[121] Moreover, several studies have shown the prognostic significance of endothelial dysfunction in patients, especially women, with "normal" coronary arteries.[122] It should be noted that the gold standard of coronary angiography has important limitations. For example, in patients with chest pain but negative catheterization, intravascular ultrasound, which assesses anatomy beyond lumen diameter, consistently shows morphological changes throughout the arterial tree.[123, 124] The current study also has a component of work-up bias as patients with a high pre-test likelihood of CAD typically proceed directly to cardiac catheterization as the first line diagnostic assessment. This limits the ability of this study to describe the full range of CPX responses from none to mild to severe disease. Given that previous investigations can be relied on for these responses, the present one may better reflect the type of patient being referred for exercise testing, providing a better representation of current clinical practice.

Despite these limitations, this study provides evidence of the potential clinical applicability of CPX in the diagnosis of CAD. Although the results raise additional questions, in particular related to the use of CPX with MPS as a gold standard in women, a few initial conclusions can be made. First, the use of CPX has a potential role in the diagnosis of CAD as has been demonstrated by this and previous studies over the past 30 years. Second, CPX can be used in an "all-comers" clinical population with mixed risk (low to high) for having CAD. Additionally, the assessment of O_2 pulse appears to have some clinical value in this patient population and for the first time a measure of ventilatory efficiency has proven to be reflective of abnormal myocardial perfusion.

A natural follow-up question is when and where CPX should be incorporated into the diagnostic work-up of patients with suspected CAD. The addition of ventilatory expired gas may not be warranted when stress MPS is performed in conjunction with standard exercise stress testing procedures. However, in centers with fewer resources that continue to solely rely on the standard exercise stress test (i.e. ECG, hemodynamics and symptomatology) to determine the likelihood of LV dysfunction secondary to myocardial ischemia, the addition of ventilatory expired gas analysis may be warranted to improve diagnostic accuracy. Additionally, the evolution of ventilatory expired gas technology has substantially reduced the space requirements and cost of this equipment, factors which certainly increase the likelihood of acceptance by clinicians operating exercise stress testing laboratories. Future research is needed to clarify this issue and determine if a paradigm shift in the diagnostic assessment of patients with suspected CAD is needed.

In conclusion, as a stand-alone procedure, the traditional exercise stress test is limited in its ability to accurately diagnose clinically significant CAD. These limitations have led to the

addition of MPS and other imaging strategies to more accurately identify those with myocardial ischemia. While this practice will certainly continue, smaller clinical centers unable to perform nuclear imaging may still have to rely of the exercise stress test as a first-line assessment of patients with suspected CAD. The results of the present study indicate the addition of CPX to the standard exercise stress test may significantly improve the ability to accurately identify males with abnormal myocardial perfusion. The diagnostic utility of exercise stress testing with CPX in females is undetermined at this time. Utilization of a gold standard diagnostic test with greater accuracy in females may be needed to address this unresolved issue. Past investigations in conjunction with the findings of the present study certainly warrants the continuation of research examining the potential diagnostic value of CPX in patients with suspected CAD.

Table 1: Baseline and Exercise Differences By MPS Result

	Negative (n=202)	Equivocal (n=69)	Mild – Severe (n=32)
Age (years)	49.5 ±10.8	50.23 ±13.1	51.8 ±12.6
Gender (% male)	46	61#	69*
BMI	29.5 ±6.2	31.5 ±6.2	33.7 ±7.8*
Number of Risk Factors	2.9 ±1.5	3.2 ±1.4^	3.7 ±1.5*
Cardiac History (% with CAD)	6.9	14.5#	21.9*
Chief Complaint (%)			
Atypical Chest Pain	67.2	66.1	51.6*
Typical Chest Pain	14.0	13.2	25.8*
SOB	8.5	4.4^	13.0*
Rest Hemodynamic Data			
HR (bpm)	73.6 ±14.4	71.6 ±14.5	76.6 ±14.5
SBP (mmHg)	133.3 ±18.9	135.1 ±17.2	137.7±32.0
DBP (mmHg)	82.6 ±10.7	82.1 ±9.9	82.5 ±11.6
Exercise Hemodynamic and Ventilatory Data			
Max HR (bpm)	152.0 ±18.9	145.5 ±20.2#	146.4 ±14.9
PPMHR (%)	89.2 ±9.8	85.9 ±11.2	87.4 ±9.7
Max SBP (mmHg)	185.2 ±25.8	182.8 ±20.9	193.3 ±28.5
Max DBP (mmHg)	88.1 ±14.8	87.0 ±17.2	90.0 ±17.0
RPP (max SBP*max HR)	28 148.2 ±5103.0	26 671.9 ±5001.2	28 369.1 ±5385.5
TM Time (sec)	435.8 ±167.0	442.7 ±159.6^	357.6 ±146.2*
RPE	14.6 ±2.7	14.7 ±2.2	14.4 ±3.9
DOE	1.7 ±1.3	1.8 ±1.3	2.0 ±1.5
Chest Pain	0.3 ±0.8	0.5 ±1.0	0.41 ±1.0
Peak RER	1.10 ±0.1	1.09 ±0.2	1.12 ±0.2
Peak VO$_2$ (mLO$_2$•kg^{-1}•min-1)	23.2 ±7.0	22.32 ±5.7	20.7 ±7.0

O$_2$ Pulse Flat Duration (sec)	70.73 ±79.0	79.3 ±97.4	61.34 ±73.0
O$_2$ Pulse$_{peak-rest}$	9.7 ±3.3	10.5 ±3.3	9.7 ±3.9
VE/VCO$_2$ slope	22.0 ±3.0	22.3 ±3.7	23.2 ±4.5
VE/VCO$_2$ slope50-75	5.2 ±6.3	5.2 ±6.7	4.4 ±6.9
OUES100	2.5 ±0.76	2.6 ±0.66	2.6 ±1.0
OUES50-75	0.27 ±1.1	0.09 ±1.1	-0.4 ±1.3*****

# p<.05 neg vs equivocal
* p<.05 neg vs mild/severe
^ p <.05 equiv vs mild/severe

Abbreviations: BMI: body mass index; CAD: coronary artery disease; SOB: shortness of breath; RHR: rest heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; PPMHR: percent predicted maximal heart rate; RPP: rate pressure product; TM: treadmill; RPE: rating of perceived exertion; DOE: dyspnea on exertion; RER: respiratory exchange ratio; OUES: oxygen uptake efficiency slope.

Table 2: Comparison of Predictive Models via ROC Analysis

|	Area Under Curve (95% CI)							
	Full Cohort (n=303)		No Beta-Blockade (n=238)		Males Only (n=157)		Females Only (n=146)	
	All	Mild-Severe	All	Mild-Severe (n=22)	All	Mild-Severe (n=22)	All	Mild-Severe (n=10)
ST Segment Depression	.49 (.42,.56)	.48 (.37,.59)	.51 (.43,.59)	.49 (.37,.62)	.48 (.38,.57)	.48 (.35,.62)	.48 (.38,.59)	.52 (.33,.72)
O_2Pulse Flat. Duration	.50 (.44,.57)	.53 (.44,.63)	.51 (.43,.59)	.54 (.43,.64)	.52 (.43,.61)	.52 (.40,.64)	.52 (.41,.62)	.45 (.29,.61)
O_2Pulse$_{Peak-Rest}$	.45 (.38,.52)	.54 (.43,.65)	.48 (.37,.53)	.50 (.36,.64)	.51 (.42,.60)	.66* (.52,.80)	.47 (.37,.58)	.46 (.25,.68)
OUES 50-75	.59* (.52,.65)	.67* (.57,.77)	.59* (.51,.67)	.65* (.52,.77)	.67* (.59,.76)	.76* (.67,.85)	.51 (.40,.62)	.49 (.26,.72)
VE/VCO$_2$ 50-75	.50 (.43,.57)	.51 (.40,.62)	.52 (.44,.60)	.55 (.42,.69)	.48 (.39,.57)	.50 (.36,.64)	.47 (.36,.58)	.44 (.25,.62)

*$p< 0.05$

61
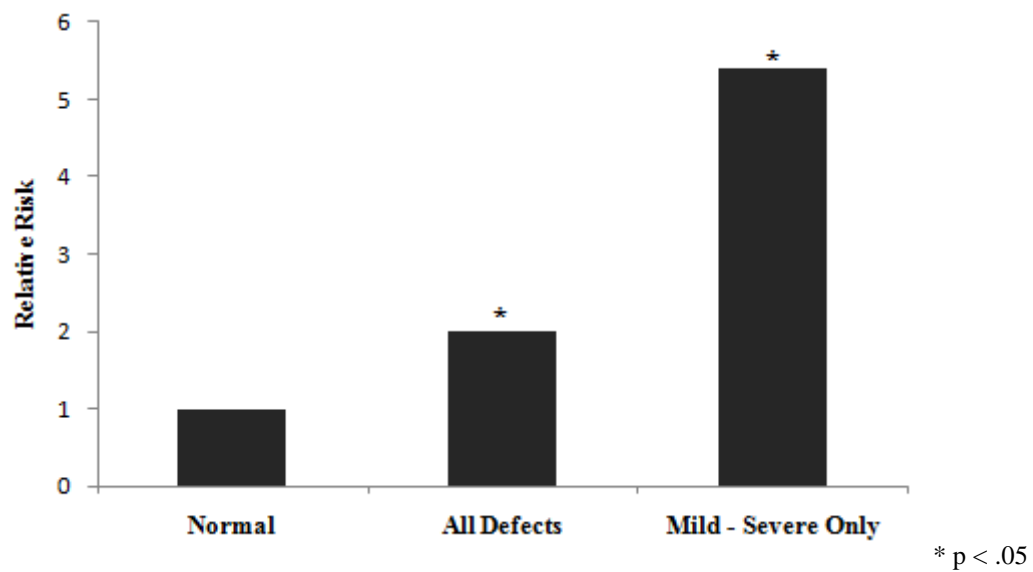
Figure 1: Relative Risk for OUES 50-75 Threshold of Zero
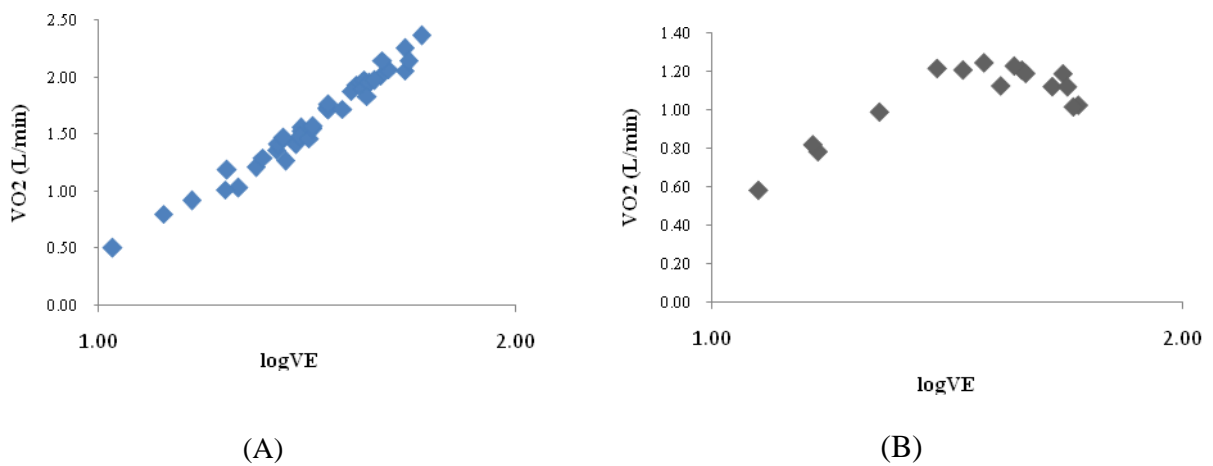
(A)	(B)
Increase (0.5) in OUES50-75 and no perfusion defect	Decrease (-3) in OUES and moderate perfusion defect

Figure 2: Examples of Change in OUES

Chapter 3: Overestimation of Aerobic Capacity with the Bruce Treadmill Protocol in Patients being Assessed for Suspected Myocardial Ischemia

ABSTRACT

Introduction: Peak oxygen consumption (VO_2) is highly prognostic for morbidity and mortality from a wide range of illnesses, including coronary artery disease (CAD). The practice of estimating aerobic capacity during traditional exercise stress testing is common as it has been shown that total treadmill time or speed and grade on the Bruce protocol predicts peak VO_2. However, the potential to overestimate peak VO_2 exists and may have significant clinical implications regarding the interpretation of exercise test data. The purpose of the present study is to investigate this issue in a large cohort of patients with suspected CAD undergoing exercise stress testing and nuclear myocardial perfusion imaging.

Methods: Three hundred and three subjects with symptoms suggestive of myocardial ischemia underwent a single photon emission computed tomography myocardial perfusion study and an exercise test with simultaneous analysis of ventilatory expired gas. Estimated VO_2 from the Bruce treadmill protocol was compared to measured VO_2. The Duke Treadmill Score (DTS) was calculated with treadmill time (DTS_{time}) and also with measured VO_2 ($DTS_{measured}$), expressed as metabolic equivalents (METs), and converted to time using an established equation.

Results: Peak measured METs was significantly lower than peak estimated METs in the whole cohort (6.5 ±1.9 vs. 8.8 ±2.8, p <0.001) as well as in female (5.7 ±1.4 and 7.8 ±2.1, p<0.001) and male (7.3 ±2.0 and 9.7 ±3.1, p<0.001) subgroups. Calculation of the DTS with measured METs resulted in a significantly lower score compared to its calculation with treadmill time (2.7 ±3.5 vs. 5.8 ±4.6, p < 0.001). The $DTS_{measured}$ and DTS_{time} for women (2.1 ±3.5 and 4.7 ±4.2, respectively, p < 0.001) were both significantly lower than for men (3.3 ±3.5 and 6.9 ±4.6,

respectively, $p < 0.001$). Receiver operating characteristic curve analysis revealed that

$DTS_{measured}$ produces a statistically significant model for diagnosing a reversible perfusion defect

in both men and women ($p<0.05$), while DTS_{time} was only diagnostic in men ($p<0.05$).

Conclusions: This study demonstrates that estimates of aerobic capacity are significantly

higher than measured values and this difference may result in a significant underestimation of

risk from all cause or cardiovascular mortality.

Introduction

The traditional exercise electrocardiogram (ECG) test, or stress test, has been a first line clinical standard for the non-invasive detection of coronary artery disease (CAD) for several decades. The Duke Treadmill Score (DTS), developed in 1987 by Mark et al.,[125] incorporating Bruce Protocol treadmill time, ST segment changes and angina into a single score, has been shown to be prognostic of future events and diagnostic of significant and/or severe coronary stenosis.[126] Even before the publication of the original DTS paper, the Bruce Protocol was the most frequently used protocol in clinical practice for the purpose of assessing individuals with suspected CAD.[127] Currently, there is evidence suggesting it is even more widely used, which is likely a consequence of the wide acceptance of the DTS.[128]

Aerobic capacity, as measured by peak oxygen consumption (VO_2) and commonly expressed in units of metabolic equivalents (METs) where 1 MET = 3.5 $mLO_2 \cdot kg^{-1} \cdot min^{-1}$, is highly prognostic for morbidity and mortality from a wide range of illnesses, including cardiovascular disease. In fact, a recent meta-analysis incorporating data from over 100,000 subjects found that for every 1 MET increase in aerobic capacity there was a 13% and 15% decrease in risk of all cause mortality and cardiovascular events, respectively.[129] Cardiopulmonary exercise testing (CPX), a technology not frequently utilized in stress testing laboratories, directly measures VO_2 thus providing accurate quantification of aerobic capacity. The total treadmill time on the Bruce protocol has been shown to predict peak VO_2,[101] however; the large degree of error associated with its estimation in this way has been demonstrated by numerous investigators.[130, 131] This is particularly true when employing a treadmill protocol with large per-stage increases in exercise intensity, such as the Bruce, in individuals who are deconditioned or have cardiovascular and/or pulmonary disease.[128, 132] Despite this significant

limitation, estimating rather than directly measuring VO_2 remains the standard. The degree of

error in estimated aerobic capacity in patients undergoing exercise stress testing is not well

characterized, nor is it known if this is clinically significant with respect to data interpretation.

Therefore, the present investigation attempts to answer the following questions: 1) is measured

VO_2 different from estimated VO_2 in a population of men and women undergoing evaluation for

possible CAD, and 2) will the difference between measured and estimated VO_2 change

diagnostic scores or prognostic risk estimates?

Methods

The current investigation prospectively assessed 303 patients who presented to the Non-

Invasive Stress Laboratory of Virginia Commonwealth University Medical Center from May

2009 to February 2010. Common indications included chest pain (65.3%), dyspnea (8%), history

of CAD (5%) syncope (1.3%), palpitations (3%) and/or abnormal ECG (2.4%). Exclusion

criteria were myocardial infarction or percutaneous coronary intervention (PCI) within three

months of testing, previous diagnosis of congestive heart failure, known left ventricular ejection

fraction <35%, evidence of moderate lung disease by pulmonary function test, moderate or

severe aortic or mitral valve stenosis, unstable angina or uncontrolled hypertension, previous

pacemaker implant or coronary artery bypass grafting, orthopedic/neurologic conditions that

limited exercise performance, and/or inability to collect interpretable ECG and nuclear imaging

data. Cardiac risk factors were recorded and included hypertension, lipid profile, tobacco use,

family history of early coronary disease, physical activity and diabetes. Physical activity

frequency, duration and intensity were measured by patient self-report. Exercise tests were

performed in the fasting state and patients were instructed to avoid all caffeine-containing food

or drink in the 4 hours prior to the test. Patients were instructed to follow the recommendation of their physician on taking prescribed medications.

The protocol was approved by the Institutional Review Board at Virginia Commonwealth University. All subjects signed an informed consent prior to inclusion in the study.

Nuclear Myocardial Perfusion Imaging Procedures

All subjects had the stress portion of a single photon emission computed tomography (SPECT) myocardial perfusion study (MPS) the same day as the standard exercise test with ventilatory expired gas analysis. However, based on referral source and/or patient characteristics, some subjects underwent the rest portion of the MPS on a different day. Briefly, two main referral sources exist for this clinic. The first is the Emergency Department (ED) from which patients are referred for follow up stress MPS after undergoing an evaluation for possible myocardial ischemia or infarction. At the time of the ED visit patients undergo rest SPECT MPS. Nearly half (48.8%) of the subjects included in the present investigation were referred through the ED. The second referral source is primary care and cardiology physicians. These patients typically have both the rest and stress portions of the study done on the same day. The remaining 51.2% of the subjects in this study were referred in this manner.

Given this, various SPECT MPS protocols are utilized depending on patient characteristics and nuclear isotope availability. During the data collection period there was a worldwide shortage of one of the commonly used nuclear isotopes, technetium 99 (aka tetrofosmin). As a substitute, thallium-201 (TL-201) was used. It has been shown that TL-201 and tetrofosmin are similar in detecting CAD.[100] All SPECT MPS were done with ECG gating (16 time frames in the heart cycle) to allow for determination of global and segmental left

ventricular function as well as for detection of perfusion abnormalities. Forty percent of the tests were done with tetrofosmin and in the remainder TL-201 was used.

Each result was categorized as the presence and extent of reversibility according to the following: 0/normal = no evidence of attenuation or reversibility or fixed defect likely due to soft tissue attenuation; 1/equivocal = small size and low grade reversible defect; 2/mildly abnormal = small size and moderate grade or moderate size and low grade reversible defect; 3/moderately abnormal = moderate size and moderate grade reversible defect; 4/severely abnormal = moderate size and high grade or large size and high grade reversible defect.

Standard Exercise Test Procedures

All exercise tests were done on a motorized treadmill (GE Healthcare Series 2000, Waukesha, WI) using the Bruce Protocol.[101] Subjects were instructed by the clinician conducting the test to rest both hands on the front handrail for support throughout the test to minimize the risk of loss of balance or falling. Exercise testing procedures outlined by the American Heart Association were followed for all assessments.[3, 102] Patients were continuously monitored by a 12-lead ECG (GE Marquette 12SL, Waukesha, WI) and hemodynamic measurements were made during each stage of the protocol. Blood pressure was measured with an automated sphygmomanometer (SunTech Tango+, Morrisville, NC) with auditory confirmation. Patients were encouraged to exercise to their maximum tolerance. Maximum heart rate (MHR) was defined as heart rate at peak exercise. Age-predicted maximum heart rate (APMHR) was calculated with the following: APMHR = 220 – age. Percent-predicted maximum heart rate (PPMHR) was calculated with the following: (MHR/APMHR)*100. Maximum systolic blood pressure (SBP) and diastolic blood pressure (DBP) were defined as

SBP and DBP at peak exercise. The following exercise test termination criteria were used:

onset of typical angina, arrhythmias (premature ventricular contractions; greater than or equal to

3 beat run of ventricular tachycardia; new onset atrial fibrillation, atrial flutter or tachycardia

with rapid response; second or third degree heart block), hypotension, bradycardia or decrease in

heart rate with same or greater workload, dyspnea, intermittent claudication, CNS symptoms,

marked hypertension, greater than 3 mm of horizontal or down sloping ST segment depression or

ST elevation $\geq$ 1 mm, and patient's request to stop.

Cardiopulmonary Exercise Test Procedures

Ventilatory expired gas was collected for each test using a metabolic cart (Vmax Encore,

SensorMedics, Yorba Linda, CA). Before each test, the equipment was calibrated in standard

fashion using reference gases and a 3-liter syringe. Ventilatory expired gas analysis data

collection began at rest and continued throughout the duration of the test. The first minute was

used to familiarize the subject to the equipment, to normalize ventilatory pattern and to allow for

collection of baseline data.

Data Analysis

Oxygen consumption (VO_2), was acquired breath-by-breath, and averaged over 30-

second intervals. Peak VO_2 is expressed as the highest 30-second averaged sample obtained

during the exercise test in $mLO_2 \bullet kg^{-1} \bullet min^{-1}$. Metabolic equivalents (METs) were calculated by

dividing peak VO_2 ($mLO_2 \bullet kg^{-1} \bullet min^{-1}$) by 3.5. Predicted VO_2 was calculated using equations

proposed by Wasserman.[133] Percent-predicted peak VO_2 was calculated by dividing measured

peak VO_2 by predicted VO_2 and multiplying by 100. Estimated METs were automatically

derived by the exercise testing software (GE Cardiac Assessment System for Exercise Testing [CASE], Waukesha, WI) and were based on the speed and grade associated with the last stage completed on the Bruce Protocol using an established regression equation for walking: [METs = $(3.5 + 2.68$ (speed) + 0.48 (speed) (%grade)/3.5].[134] Subjects completing ≥ 2 minutes of a given stage of the Bruce protocol were awarded the full estimated METs value. For subjects completing <2 minutes of a given stage, the estimated METs value was determined through linear interpolation. For a separate analysis, subjects completing >9 minutes (i.e. beginning, completing or surpassing stage 4) of the Bruce protocol, peak METs were manually calculated by this study's investigators using an established regression equation for jogging/running: [METs = $(3.5 + 5.36$ (speed) + 0.24 (speed) (%grade)/3.5].[134] For subjects completing <2 minutes of stage 4 of 5, the estimated METs value was manually determined through linear interpolation. The discrepancy in aerobic capacity, expressed as VO_2 or METs, was calculated as the difference in peak estimated and peak measured values. Finally, linear regression using maximum estimated METs was used to predict maximum predicted METs.

The Duke Treadmill Score (DTS) was calculated in two ways. First, it was calculated with treadmill time (TM) according to the following: DTS = TM time − (5 * ST segment deviation) − (4 * angina index). It was also calculated with measured VO_2, expressed as METs. The following conversion was then used to transform measured METs to treadmill time: TM time = (METs/2.2)+1.3.[16] In both cases, ST segment deviation was measured in millimeters (by an experienced cardiologist) and angina index was scored according to the following: 1= no chest pain, 2 = non-limiting chest pain, 3 = exercise-limiting chest pain. Risk estimates were determined by DTS score according to the following: low risk = $\geq$ +5, moderate risk = -10 − 4, and high risk = $\leq$ -11.[125]

<u>Statistical Analysis</u>

Statistical analysis was performed using SPSS 17.0 (SPSS, Chicago, IL). Unpaired t-testing compared differences in key baseline and exercise test variables according to sex. Paired student's t-test was used to compare measured and estimated aerobic capacity and DTS in the whole cohort. A mixed model two-way analysis of variance (ANOVA) assessed differences between measured and estimated expressions of aerobic capacity and DTS (within subject factors) according to sex (between subject factors). Four separate two-way ANOVA tests were performed to assess the discrepancy between peak estimated and measured METs in both males and females according to: 1) age, 2) physical activity status, 3) MPS result, and 4) total treadmill time. Both main and interaction effects were assessed. Paired student's t-test was again used to compare the discrepancy between peak estimated and measured METs using the walking vs. jogging/running equation in the subgroup of subjects who completed >9 minutes of the Bruce treadmill protocol. The Pearson's test was used to determine correlation between age and the discrepancy between peak estimated and measured METs. Receiver operating characteristic (ROC) analysis was used to test the ability of the DTS, calculated with TM time or measured METs, to diagnose a positive MPS. All statistical tests with a p-value <0.05 were considered significant. All means are expressed ± standard deviation.

Results

Three hundred and three subjects, 157 men and 146 women, completed the protocol. The average age was 49.9 ±11.6 and was not different between men and women (50.6 ±12.3 vs. 49.4 ±10.7, p=0.30). Likewise, mean BMI was 30.4 ±6.5 kg/m^2 and was similar between the genders (30.0 ±6.5 vs. 30.9 ±6.6, p=0.21). The majority of subjects (86.1%) had no history of heart

disease. Of these, 8.3% had undergone cardiac catheterization without intervention. Ten percent

of subjects were known to have CAD: 8.9% percent had a previous PCI, and 1.1% had a

myocardial infarction (MI) without intervention. Electrical abnormalities and mild valvular

disorders were present in 3.9% of the subjects. The majority (73.6%) were taking prescribed

medications on the day of the test. Of these, slightly more than half (55.1%) were taking an anti-

hypertensive, 31.4% were taking a lipid-lowering agent, 28.1% were taking aspirin and 11.2%

were taking a medication for diabetic management. More than half (57.4%) reported no regular

physical activity. Another 27.7% reported exercising less than 3 days per week and only 14.8 %

reported participation in exercise on 4 days or more per week. The mean number of traditional

cardiovascular risk factors was 3.0 ±1.5.

Two hundred and two subjects (66.7%) had a normal myocardial perfusion study, 69

(22.8%) subjects had an equivocal study and 32 (10.5%) had a mildly, moderately or severely

abnormal MPS. Of those with an abnormal result, the percent of myocardium involved ranged

from 1-14%, with a mean of 4.39% ±3.31%. The majority of the defects were small in size

(72.5%) and low in grade (84.2%). Wall motion abnormalities were present in 7.6% of those

with an abnormal stress MPS. The frequency of negative, equivocal and positive MPS was

different among men and women (93, 42, 22 vs. 109, 27, 10, respectively; p < .01).

Maximal heart rate was significantly lower in females compared to males but no

difference between percent-predicted maximal heart rate was evident. Likewise, maximum

systolic blood pressure was greater in males. Males exercised significantly longer than females

(Table 1). Peak measured aerobic capacity was significantly lower than peak estimated aerobic

capacity in the whole cohort, a trend that persisted in both men and women (Figure 1).

Moreover, the discrepancy in estimated and measured aerobic capacity was significantly greater

72

for men vs. women. In the overall group, 74% of the subjects had at least a one MET

discrepancy between estimated and measured aerobic capacity while 57% had at least a two

MET discrepancy. Percent-predicted VO_2 derived from estimated aerobic capacity was

significantly greater than percent-predicted VO_2 derived from measured aerobic capacity and the

difference was greater in women than men (Table 1). Linear regression using estimated METs to

predict measured METs was significant ($R^2 = 0.58$, SEE = 1.24, $p < 0.001$) , however estimated

METs only accounted for 58% of the variability in actual METs. Furthermore, the standard error

of the estimate was greater than 1 MET.

The discrepancy between peak measured and estimated METs was not different

according to physical activity patterns, myocardial perfusion imaging result or categorical age

grouping. There was, however, a statistically significant, albeit weak, positive correlation

between MET discrepancy and age expressed continuously ($r = 0.12$, $p < 0.05$). There was a

significant main effect of treadmill time on METs discrepancy with those exercising > 9 minutes

having a larger discrepancy than those exercising less than 9 minutes. This significant result was

consistent in both males and females and no interaction effect between sex-based subgroups. In

the aforementioned analysis, peak estimated METs were derived from the walking equation in all

subjects irrespective of treadmill time (Table 2).

For those completing > 9 minutes, the treadmill time analysis was repeated with

estimated peak METs recalculated with the jogging/running equation. The discrepancy between

peak measured and the newly estimated METs was still significantly greater in subjects

completing >9 minutes in the overall cohort (-3.2 ±1.5 vs. -1.7 ±1.5, p<0.001) as well as in males

(-3.1 ±1.5 vs. -1.6 ±1.6, p<0.001) and females (-3.5 ±1.3 vs.-1.9 ±1.4, p<0.001). However, the

discrepancy was significantly reduced when the jogging/running equation was used to calculate peak estimated METs compared to values derived from the walking equation (Figure 2).

For the whole cohort, calculation of the DTS with measured METs ($DTS_{measured}$) resulted in a significantly lower (i.e. worse) score than when it was calculated with time (DTS_{time}), a trend that again persisted in gender subgroups. Moreover, both DTS calculations were significantly higher in males compared to females (Table 1). In the whole cohort, the frequency of being classified in either a low, moderate or high risk category was significantly different for DTS_{time} vs. $DTS_{measured}$ (216, 84, 3 vs. 81, 219, 3 respectively, $p<0.001$). $DTS_{measured}$ resulted in women being reclassified into a higher risk category with greater frequency than men. Specifically, 78 women were reclassified from low to moderate or moderate to high risk compared to 60 men ($p<.001$). ROC analysis revealed that both $DTS_{measured}$ and DTS_{time} were able to elicit predictive models in males (AUC = 0.61 [95% CI: 0.52, 0.70] vs. AUC = 0.60 [95% CI: 0.51, 0.69]; $p<0.05$ for both). Alternately, only $DTS_{measured}$ produced a statistically significant model for predicting MPS result in females ($AUC_{DTSmeasured}$ = 0.62 [95% CI: 0.52, 0.72], $p <0 .05$ vs. $AUC_{DTStime}$ = 0.56 [0.45, 0.66], $p=0.32$).

Discussion

Numerous studies have described several variables that should be taken into account in order to accurately estimate VO_2. Protocol selection is consistently identified as being one of the primary variables. Appropriate protocol selection is based on age, functional mobility, disease status and physical activity patterns. The Bruce Protocol utilizes stages which introduce a 2-3 estimated METs increase in exercise intensity every three minutes. This large per-stage increase in work load has been shown to result in overestimation of exercise capacity.[135, 136] The results

of the present study support previous investigations in that aerobic capacity is significantly overestimated in both male and female subjects undergoing an exercise stress test that employs the Bruce treadmill protocol. The vast majority of patients in the current study were sedentary with 85% reporting less than the recommended daily amount of physical activity (4 days or more weekly) although there was no significant difference in the METs discrepancy between those who did or did not report this amount of regular exercise. Age and peak VO_2 are inversely related and therefore in older subjects less aggressive protocols are recommended.[137] Similarly the presence of disease may necessitate a more conservative protocol but, again, in this study the significant difference in estimated and measured METs was not different regardless of MPS result. Finally, tests longer than 9 minutes in duration were significantly more likely to produce a greater peak METs discrepancy. A contributing factor to this time-dependent difference may be the equation used to estimate METs. This equation, used in the current study and in most stress testing labs, is based on a treadmill speed and grade that will result in walking throughout the entire test. However during the 4th ($\geq$9 minutes) or 5[th] ($\geq$12 minutes) stage of the Bruce Protocol, a number of patients will begin to jog or run to keep up with the pace (4.2 mph/16% grade and 5.0 mph/18% grade, respectively) of the belt. An established equation that accounts for this alteration in gait pattern exists and its use may likely be warranted.[134] Future iterations of software would benefit from flexibility in the use of the most appropriate equation based on the running or walking status of the patient during the test. Even so, while the results of the current study indicate use of the jogging/running equation for those completing > 9 minutes of the Bruce Protocol significantly reduces the peak METs discrepancy, a substantial overestimation appears to persist. Therefore, development of alternate regression equations to better estimate the oxygen requirement of jogging or running may be necessary.

Another significant contributor to the difference in measured and estimated METs is the use of the front handrail by all subjects in this study. Handrail use decreases sub-maximal VO_2 and HR and impacts estimates of exercise capacity for any given treadmill time.[138, 139] Moreover, treadmill time is increased when handrail use is allowed. The impact of handrail support was recognized as contributing to the variability in exercise duration during the development of the Bruce Protocol itself and therefore, was not allowed, although it is not clear if the creators of the DTS followed this same convention. In the present investigation the degree of handrail assist was not assessed and can therefore be viewed as a limitation of this study. The lack of control for handrail use was, however, prospectively and intentionally conceived in order to capture a more accurate reflection of current clinical practice patterns in an exercise stress testing laboratory. While published guidelines advocate for the elimination/minimization of handrail use during exercise testing on a treadmill,[137] it is likely that the use of handrails is commonplace[140] in clinical practice and will persist due to perceived safety concerns. A way to objectively measure and account for the impact of handrail use on estimated VO_2 would therefore be an important contribution, allowing for clinicians to more accurately quantify a subject's aerobic capacity.

The current study reveals that the DTS calculated with treadmill time fails to indentify a positive MPS result in women while the converse was true in men. Even so, while statistically significant, the diagnostic model for DTS calculated with treadmill time in males was relatively weak. Additionally, when measured VO_2 was used to calculate DTS a statistically significant, albeit weak, model for both men and women is elucidated. The explanation for this may lie in the differences between the cohort of patients included in the current investigation and the one in which the tool was developed. First, the original cohort was mostly men.[125] In the later

diagnostic validation of the DTS the vast majority of subjects who had a high risk score were also men (91%) and the DTS was shown to be most effective at identifying significant or severe disease.[141] In the current study, there was a very low incidence of severe perfusion defects and roughly half of the patients were female. Therefore, it may be the DTS is a more robust diagnostic tool in cohorts more closely approximated to the characteristics of the subjects in which it was originally developed. From a prognostic standpoint, the DTS is frequently used to define risk for future adverse events in subjects undergoing an exercise stress test. The results presented here indicate the overestimation of aerobic capacity from peak estimated METs may falsely lower risk estimates for a large number of individuals undergoing this examination, which may have important implications for medical management.

An error in the estimation of aerobic capacity itself has several important implications without consideration of other variables obtained from exercise testing. First, overestimation of exercise capacity results in an underestimation of risk. In this study true aerobic exercise capacity was overestimated by at least 1 MET in approximately three-quarters of the subjects assessed. Moreover, true aerobic capacity was overestimated by at least 2 METs in more than half of the subjects assessed. This may have significant implications for the underestimation of future risk for morbidity and mortality according to aerobic capacity.[129] Admittedly, the recent meta-analysis by Kodama et al.[129] clearly demonstrated an estimated calculation of peak METs is highly prognostic despite its potential to overestimate true aerobic capacity. However, it is unknown if a more accurate quantification of aerobic capacity would further improve the already robust prognostic value of aerobic capacity estimated from treadmill speed, grade and/or time. This is an important issue for future investigations given the clear clinical value in assessing aerobic exercise capacity in numerous populations.[137] Like the DTS, an underestimation of risk

77

through an overestimation of aerobic capacity alone may also impact therapeutic decisions. In those with an exercise capacity of 10 METs or more, prognosis is considered the same for medical therapy or coronary artery bypass surgery.[3] In the present study, 117 subjects achieved at least 10 METs when they were estimated whereas only 15 subjects achieved the same important threshold when peak METs were measured (p<0.001). Alternately, a less than 5 MET exercise capacity is a well-recognized threshold indentifying those patients with a particularly poor prognosis[3] and significantly more patients in this investigation failed to surpass this threshold when using measured compared to estimated values (72 vs. 20, p <0.001). Finally, regular aerobic exercise training is a well-recognized lifestyle intervention with a positive impact on morbidity and mortality.[142] Exercise stress testing affords clinicians the opportunity to discuss the initiation/maintenance of an aerobic exercise regimen. The appropriate moderate exercise intensity range (typically 3-6 METs) should be based upon the patient's test result. An exercise program developed from an inflated estimate of aerobic capacity could conceivably result in the recommendation to engage in activities that would be at a much greater intensity than intended.

A limitation of this study is the lack of cardiac catheterization data to confirm the MPS results. This is due to the relatively mild perfusion defects detected and the lower risk profile of many of the included subjects resulting in the clinical decision to defer further invasive testing. However, previous research has demonstrated a positive MPS is a significant predictor of adverse events regardless of catheterization findings.[143] Moreover, several studies have shown the prognostic significance of endothelial dysfunction in patients, especially women, with "normal" coronary arteries.[144] The limitations of coronary angiography have been described extensively.[38] For example, in patients with chest pain but negative catheterization, intravascular

ultrasound, which assesses anatomy beyond lumen diameter, consistently show morphological

changes throughout the arterial tree.[145, 146]

In conclusion, this study demonstrates the estimation of peak VO_2 can lead to clinically

meaningful errors in the assessment of patients with suspected CAD referred for exercise stress

testing. Specifically, estimation of aerobic capacity portrays an exaggerated level of fitness and

diminished risk for future adverse events. The accurate quantification of exercise capacity is of

utmost importance given its strong association with outcome in multiple disease conditions.

Cardiopulmonary exercise testing is the only way to directly measure exercise capacity, but

currently CPX is not a standard part of a functional capacity assessment. This may be in part due

to the size and expense of the equipment needed; however, modern metabolic carts are smaller to

the point of being nearly portable and have become more affordable. Moreover, many more

professionals are becoming expert in the performance of this test, removing the barrier of a lack

of trained personnel. Despite this, the estimation of exercise capacity from the standard exercise

stress test will undoubtedly continue and therefore efforts should be made to: 1) improve the

administration of these tests with the goal of better individualization (i.e. selection of an

appropriate exercise protocol) and closer adherence to established guidelines (i.e. minimization

of handrail use when possible),[147] 2) improve the ability to quantify estimated aerobic capacity

through exercise time and/or workload by developing regression equations with greater

precision, and 3) ensure future iterations of exercise testing software integrate the most accurate

means of estimating aerobic capacity with automated flexibility in the regression equations used

(i.e. transition from walking to jogging/running).

Table 1: Exercise and Ventilatory Data

	Whole Cohort	Males	Females
Max HR (bpm)	150 ±19.0	147.8 ±19.2*	152.3 ±18.6
PPMHR (%)	88.2 ±10.2	87.4 ±10.7	89.1 ±9.6
Max SBP (mmHg)	185.5 ±25.1	191.1 ±24.8*	179.6 ±24.2
Max DBP (mmHg)	88.1 ±15.6	87.9 ±16.5	88.2 ±14.6
TM Time (sec)	429.1 ±164.6	481.5 ±176.1*	372.8 ±130.2
Peak VO$_{2estimated}$ (mL•kg^{-1}•min^{-1})	30.7 ±9.8#	33.7 ±10.8*,#	27.4 ±7.3#
Peak VO$_{2measured}$ (mL•kg^{-1}•min^{-1})	22.8 ±6.7	25.5 ±7.1*	19.9 ±4.8
% Predicted VO$_{2(measured/predicted)}$*100	95.3 ±26.7#	91.7 ±27.0*,#	99.2 ±25.9#
% Predicted VO$_{2 (estimated/predicted)}$*100	129.2 ±42.0	122.5 ±41.2*	136.4 ±41.3
Peak METs$_{estimated}$	8.8 ±2.8#	9.6 ±3.1*,#	7.8 ±2.0#
Peak METs$_{measured}$	6.5 ±1.9	7.3 ±2.0*	5.7 ±1.4
DTS$_{measured}$	2.7 ±3.5#	3.3 ±3.5*,#	2.1 ±3.5#
DTS$_{time}$	5.8 ±4.6	6.9 ±4.6*	4.7 ±4.2

# $p < .001$ estimated vs. measured calculation of aerobic capacity

* $p < .05$ males vs. females

Abbreviations: HR: heart rate; bpm: beats per minute; PPMHR: percent predicted maximum heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; mmHg : millimeters mercury; TM: treadmill; sec: seconds; VO$_2$: ventilatory oxygen consumption; METs: metabolic equivalents; DTS: Duke Treadmill Score.

Table 2: Peak MET Discrepancy Based on Gender Considering Age, Physical Activity, MPS Result and Treadmill Time

|		All (n=303)	Males (n=157)	Females (n=146)
Age (years)	< 40	-2.8 ±2.2 (n=51)	-3.2 ±2.5 (n=28)	-2.2 ±1.7 (n=23)
	40-60	-2.2 ±1.9 (n=183)	-2.3 ±2.2 (n=87)	-2.2 ±1.6 (n=96)
	>60	-2.0 ±2.0 (n=69)	-2.0 ±2.3 (n=42)	-2.1 ±1.4 (n=27)
Physical Activity Status (days/week)	0-3	-2.1 ±1.9 (n=175)	-2.1 ±2.2 (n=79)	-2.1 ±1.6 (n=96)
	4-7	-2.5 ±2.1 (n=128)	-2.6 ±2.3(n=78)	-2.3 ±1.6 (n=50)
MPS Result	Neg./Equiv.	-2.3 ±2.0 (n=271)	-2.5 ±2.4 (n=135)	-2.2 ±1.6 (n=136)
	Mild-Severe	-1.6 ±1.5 (n=32)	-1.3 ±1.4 (n=22)	-2.3 ±1.7 (n=10)
TM Time (minutes)	≤9	-1.7 ±1.5 (n=237)*	-1.6 ±1.6* (n=105)	-1.9 ±1.4 (n=132)*
	>9	-4.2 ±1.6 (n=66)	-4.2 ±1.7 (n=52)	-4.1 ±1.2 (n=14)

* $p < 0.001$ METs discrepancy ≤9 vs. >9
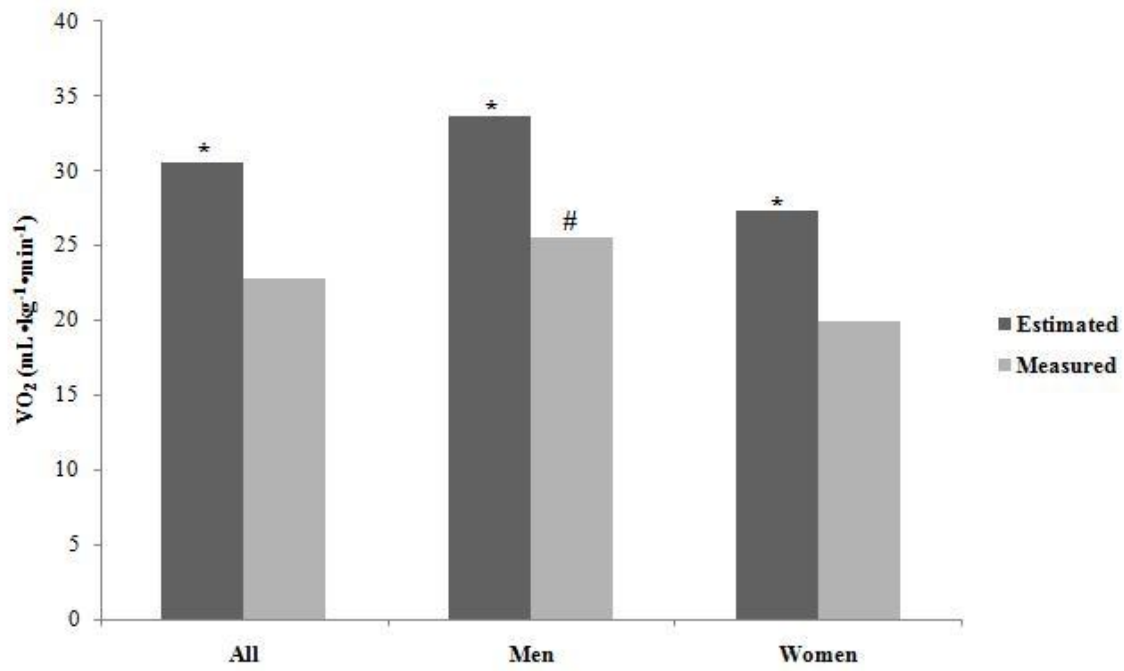
Figure 1: Comparison of Estimated and Measured VO$_2$

*p <0 .01 estimated vs. measured
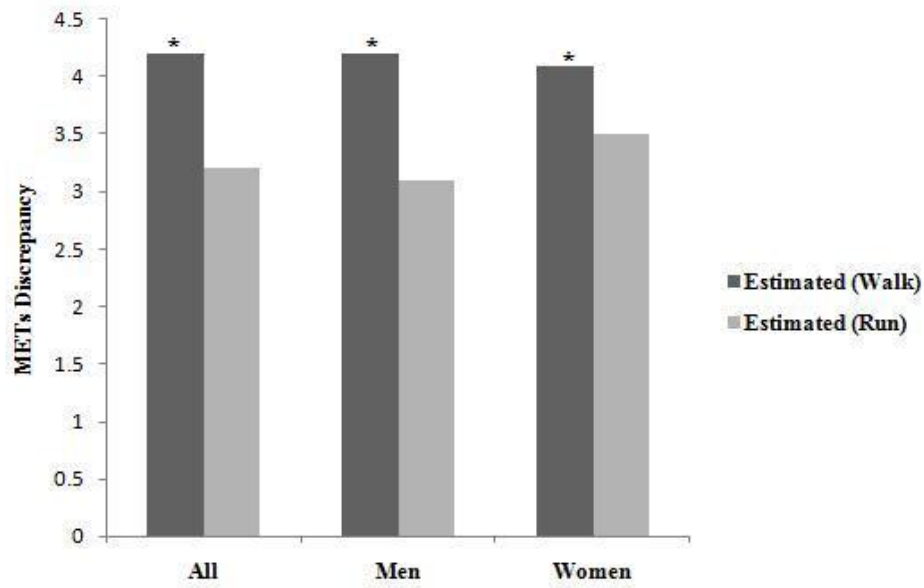**#p < 0.01 men vs. women**

Figure 2: Peak METs Discrepancy Using the Walking vs. the Jogging/Running Equation

*p < 0.01 walking vs. jogging/running

Reference List

(1) Lloyd-Jones D, Adams R, Carnethon M et al. Heart Disease and Stroke Statistics--2009 Update: A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009 January 27;119(3):e21-181.

(2) Vivekananthan DP, Blackstone EH, Pothier CE, Lauer MS. Heart rate recovery after exercise is apredictor of mortality, independent of the angiographic severity of coronary disease. *Journal of the American College of Cardiology* 2003 September 3;42(5):831-8.

(3) Gibbons RJ, Balady GJ, Timothy BJ et al. ACC/AHA 2002 guideline update for exercise testing: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *J Am Coll Cardiol* 2002 October 16;40(8):1531-40.

(4) Arena R, Myers J, Guazzi M. The clinical and research applications of aerobic capacity and ventilatory efficiency in heart failure: an evidence-based review. *Heart Fail Rev* 2008 June 1;13(2):245-69.

(5) Arena R, Myers J, Abella J et al. Development of a Ventilatory Classification System in Patients With Heart Failure. *Circulation* 2007 April 23;CIRCULATIONAHA.

(6) Francis DP, Shamim W, Davies LC et al. Cardiopulmonary exercise testing for prognosis in chronic heart failure: continuous and independent prognostic value from VE/VCO(2)slope and peak VO(2). *Eur Heart J* 2000 January;21(2):154-61.

(7) O'Neill JO, Young JB, Pothier CE, Lauer MS. Peak Oxygen Consumption as a Predictor of Death in Patients With Heart Failure Receiving {beta}-Blockers. *Circulation* 2005 May 10;111(18):2313-8.

(8) Corra U, Mezzani A, Bosimini E, Scapellato F, Imparato A, Giannuzzi P. Ventilatory response to exercise improves risk stratification in patients with chronic heart failure and intermediate functional capacity. *Am Heart J* 2002 March;143(3):418-26.

(9) Martinez FJ, Stanopoulos I, Acero R, Becker FS, Pickering R, Beamis JF. Graded comprehensive cardiopulmonary exercise testing in the evaluation of dyspnea unexplained by routine evaluation. *Chest* 1994 January;105(1):168-74.

(10) Weisman IM, Zeballos RJ. Clinical evaluation of unexplained dyspnea. *Cardiologia* 1996 July;41(7):621-34.

(11) Milani RV, Lavie CJ, Mehra MR. Cardiopulmonary exercise testing: how do we differentiate the cause of dyspnea? *Circulation* 2004 July 27;110(4):e27-e31.

(12) Messner-Pellenc P, Ximenes C, Brasileiro CF, Mercier J, Grolleau R, Prefaut CG. Cardiopulmonary exercise testing. Determinants of dyspnea due to cardiac or pulmonary limitation. *Chest* 1994 August;106(2):354-60.

(13) Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. *Circulation* 2001 July 24;104(4):429-35.

(14) Sun X, Hansen JE, Oudiz RJ, Wasserman K. Gas Exchange Detection of Exercise-Induced Right-to-Left Shunt in Patients with Primary Pulmonary Hypertension. *Circulation* 2002;105:54-60.

(15) Yasunobu Y, Oudiz RJ, Sun XG, Hansen JE, Wasserman K. End-tidal PCO2 abnormality and exercise limitation in patients with primary pulmonary hypertension. *Chest* 2005 May;127(5):1637-46.

(16) Froelicher VF, Myers J. *Exercise and the Heart*. Fifth ed. Saunders Elsevier; 2010.

(17) Opie LH. Fuels, aerobic and anaeorbic metabolism. In: Weinberg R, Bersin J, Aversa F, editors. *Heart Physiology, From Cell to Circulation*.Philadelphia: Lippincot Williams and Wilkins; 2004. p. 306-54.

(18) Opie LH. Cardiac Output and Exercise. *The Heart:Physiology,from the Cell to Circulation*.Philadelphia: Lippincott-Raven; 1998. p. 447-73.

(19) Chilian WM, Eastham CL, Marcus ML. Microvascular distribution of coronary vascular resistance in beating left ventricle. *Am J Physiol* 1986 October;251(4 Pt 2):H779-H788.

(20) Delp MD, Laughlin MH. Regulation of skeletal muscle perfusion during exercise. *Acta Physiol Scand* 1998 March;162(3):411-9.

(21) Duncker DJ, Bache RJ. Regulation of coronary blood flow during exercise. *Physiol Rev* 2008 July;88(3):1009-86.

(22) Opie LH. *Heart Physiology, From Cell to Circulation*. Fourth ed. Lippincott Williams & Wilkins; 2004.

(23) Adabag AS, Grandits GA, Prineas RJ, Crow RS, Bloomfield HE, Neaton JD. Relation of heart rate parameters during exercise test to sudden death and all-cause mortality in asymptomatic men. *Am J Cardiol* 2008 May 15;101(10):1437-43.

(24) Lauer MS, Francis GS, Okin PM, Pashkow FJ, Snader CE, Marwick TH. Impaired chronotropic response to exercise stress testing as a predictor of mortality. *Journal of the American Medical Association* 1999 February 10;281(6):524-9.

(25) Ekstrom-Jodal B, Haggendal E, Malmberg R, Svedmyr N. The effect of adrenergic - receptor blockade on coronary circulation in man during work. *Acta Med Scand* 1972 March;191(3):245-8.

(26) Vatner SF, Higgins CB, Franklin D, Braunwald E. Role of tachycardia in mediating the coronary hemodynamic response to severe exercise. *J Appl Physiol* 1972 March;32(3):380-5.

(27) Jorgensen CR, Wang K, Wang Y, Gobel FL, Nelson RR, Taylor H. Effect of propranolol on myocardial oxygen consumption and its hemodynamic correlates during upright exercise. *Circulation* 1973 December;48(6):1173-82.

(28) Horwitz LD, Atkins JM, Leshin SJ. Role of the Frank-Starling mechanism in exercise. *Circ Res* 1972 December;31(6):868-75.

(29) Poliner LR, Dehmer GJ, Lewis SE, Parkey RW, Blomqvist CG, Willerson JT. Left ventricular performance in normal subjects: a comparison of the responses to exercise in the upright and supine positions. *Circulation* 1980 September;62(3):528-34.

(30) Duncker DJ, Van Zon NS, Crampton M, Herrlinger S, Homans DC, Bache RJ. Coronary pressure-flow relationship and exercise: contributions of heart rate, contractility, and alpha 1-adrenergic tone. *Am J Physiol* 1994 February;266(2 Pt 2):H795-H810.

(31) Gianrossi R, Detrano R, Mulvihill D et al. Exercise-induced ST depression in the diagnosis of coronary artery disease. A meta-analysis. *Circulation* 1989 July;80(1):87-98.

(32) Lucas FL, DeLorenzo MA, Siewers AE, Wennberg DE. Temporal trends in the utilization of diagnostic testing and treatments for cardiovascular disease in the United States, 1993-2001. *Circulation* 2006 January 24;113(3):374-9.

(33) *Textbook of Cardiovascular Medicine*. Third ed. Lipincott Williams & Wilkins; 2007.

(34) Kim C, Kwok YS, Saha S, Redberg RF. Diagnosis of suspected coronary artery disease in women: a cost-effectiveness analysis. *Am Heart J* 1999 June;137(6):1019-27.

(35) Garber AM, Solomon NA. Cost-effectiveness of alternative test strategies for the diagnosis of coronary artery disease. *Ann Intern Med* 1999 May 4;130(9):719-28.

(36) Kuntz KM, Fleischmann KE, Hunink MG, Douglas PS. Cost-effectiveness of diagnostic strategies for patients with chest pain. *Ann Intern Med* 1999 May 4;130(9):709-18.

(37) Scanlon PJ, Faxon DP, Audet AM et al. ACC/AHA guidelines for coronary angiography. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on Coronary Angiography). Developed in collaboration with the Society for Cardiac Angiography and Interventions. *J Am Coll Cardiol* 1999 May;33(6):1756-824.

(38) Topol EJ, Nissen SE. Our preoccupation with coronary luminology. The dissociation between clinical and angiographic findings in ischemic heart disease. *Circulation* 1995 October 15;92(8):2333-42.

(39) Upton MT, Rerych SK, Newman GE, Port S, Cobb FR, Jones RH. Detecting abnormalities in left ventricular function during exercise before angina and ST-segment depression. *Circulation* 1980 August;62(2):341-9.

(40) Ehsani AA, Biello D, Seals DR, Austin MB, Schultz J. The effect of left ventricular systolic function on maximal aerobic exercise capacity in asymptomatic patients with coronary artery disease. *Circulation* 1984 October;70(4):552-60.

(41) Koike A, Itoh H, Taniguchi K, Hiroe M. Detecting abnormalities in left ventricular function during exercise by respiratory measurement. *Circulation* 1989 December;80(6):1737-46.

(42) Koike A, Hiroe M, Adachi H et al. Cardiac output-O2 uptake relation during incremental exercise in patients with previous myocardial infarction. *Circulation* 1992 May;85(5):1713-9.

(43) Koike A, Hiroe M, Adachi H et al. Oxygen uptake kinetics are determined by cardiac function at onset of exercise rather than peak exercise in patients with prior myocardial infarction. *Circulation* 1994 November;90(5):2324-32.

(44) Meyer K, Samek L, Pinchas A, Baier M, Betz P, Roskamm H. Relationship between ventilatory threshold and onset of ischaemia in ECG during stress testing. *Eur Heart J* 1995 May;16(5):623-30.

(45) Klainman E, Kusniec J, Stern J, Fink G, Farbstein H. Contribution of cardiopulmonary indices in the assessment of patients with silent and symptomatic ischemia during exercise testing. *Int J Cardiol* 1996 March;53(3):257-63.

(46) Lele SS, Macfarlane D, Morrison S, Thomson H, Khafagi F, Frenneaux M. Determinants of exercise capacity in patients with coronary artery disease and mild to moderate systolic dysfunction. Role of heart rate and diastolic filling abnormalities. *Eur Heart J* 1996 February;17(2):204-12.

(47) Zafrir N, Fink G, Klainman E, Sulkes J, Spitzer S. Relation between aerobic capacity and extent of myocardial ischemia in patients with normal cardiac function. *Am Heart J* 1999 December;138(6 Pt 1):1088-92.

(48) Bigi R, Desideri A, Rambaldi R, Cortigiani L, Sponzilli C, Fiorentini C. Angiographic and prognostic correlates of cardiac output by cardiopulmonary exercise testing in patients with anterior myocardial infarction. *Chest* 2001 September;120(3):825-33.

(49) Klainman E, Fink G, Lebzelter J, Krelbaumm T, Kramer MR. The Relationship Between Left Ventricular Function Assessed by Multigated Radionuclide Test and

Cardiopulmonary Exercise Test in Patients With Ischemic Heart Disease. *Chest* 2002 March 1;121(3):841-5.

(50) Belardinelli R, Lacalaprice F, Carle F et al. Exercise-induced myocardial ischaemia detected by cardiopulmonary exercise testing. *Eur Heart J* 2003 July;24(14):1304-13.

(51) Bussotti M, Apostolo A, Andreini D, Palermo P, Contini M, Agostoni P. Cardiopulmonary evidence of exercise-induced silent ischaemia. *Eur J Cardiovasc Prev Rehabil* 2006 April;13(2):249-53.

(52) Munhoz EC, Hollanda R, Vargas JP et al. Flattening of oxygen pulse during exercise may detect extensive myocardial ischemia. *Med Sci Sports Exerc* 2007 August;39(8):1221-6.

(53) Ajisaka R, Watanabe S, Yamanouchi T, Masuoka T, Sugishita Y. Effect of percutaneous transluminal coronary angioplasty on exercise ventilation in patients with coronary artery disease and normal left ventricular function. *Am Heart J* 1996 July;132(1 Pt 1):48-53.

(54) Klainman E, Fink G, Lebzelter J, Zafrir N. Assessment of functional results after percutaneous transluminal coronary angioplasty by cardiopulmonary exercise test. *Cardiology* 1998 May;89(4):257-62.

(55) Adachi H, Koike A, Niwa A et al. Percutaneous transluminal coronary angioplasty improves oxygen uptake kinetics during the onset of exercise in patients with coronary artery disease [see comments]. *Chest* 2000 August;118(2):329-35.

(56) Inbar O, Yamin C, Bar-On I, Nice S, David D. Effects of percutaneous transluminal coronary angioplasty on cardiopulmonary responses during exercise. *J Sports Med Phys Fitness* 2008 June;48(2):235-45.

(57) Contini M, Andreini D, Agostoni P. Cardiopulmonary exercise test evidence of isolated right coronary artery disease. *Int J Cardiol* 2006 November 10;113(2):281-2.

(58) Chaudry S, Arena R, Wasserman K et al. Exercise-Induced Myocardial Ischemia Detected by Cardiopulmonary Exercise Testing. Am J Cardiol. In press 2008.

(59) Belardinelli R, Purcaro A. Effects of trimetazidine on the contractile response of chronically dysfunctional myocardium to low-dose dobutamine in ischaemic cardiomyopathy. *Eur Heart J* 2001 December;22(23):2164-70.

(60) Belardinelli R, Lacalaprice F, Faccenda E, Volpe L. Trimetazidine potentiates the effects of exercise training in patients with ischemic cardiomyopathy referred for cardiac rehabilitation. *Eur J Cardiovasc Prev Rehabil* 2008 October;15(5):533-40.

(61) Castro RR, Porphirio G, Serra SM, Nobrega AC. Cholinergic stimulation with pyridostigmine protects against exercise induced myocardial ischaemia. *Heart* 2004 October;90(10):1119-23.

(62) Tiano L, Belardinelli R, Carnevali P, Principi F, Seddaiu G, Littarru GP. Effect of coenzyme Q10 administration on endothelial function and extracellular superoxide dismutase in patients with ischaemic heart disease: a double-blind, randomized controlled study. *Eur Heart J* 2007 September;28(18):2249-55.

(63) Ashley E, Myers J, Froelicher V. Exercise testing scores as an example of better decisions through science. *Med Sci Sports Exerc* 2002 August;34(8):1391-8.

(64) Arena R, Guazzi M, Myers J. Prognostic value of end-tidal carbon dioxide during exercise testing in heart failure. *Int J Cardiol* 2007 April 12;117(1):103-8.

(65) Arena R, Peberdy MA, Myers J, Guazzi M, Tevald M. Prognostic value of resting end-tidal carbon dioxide in patients with heart failure. *International Journal of Cardiology*In Press, Corrected Proof.

(66) Waraich S, Sietsema KE. Clinical cardiopulmonary exercise testing: patient and referral characteristics. *J Cardiopulm Rehabil Prev* 2007 November;27(6):400-6.

(67) Albouaini K, Egred M, Alahmar A, Wright DJ. Cardiopulmonary exercise testing and its application. *Heart* 2007 October 1;93(10):1285-92.

(68) Piepoli MF, Corra U, Agostoni PG et al. Statement on cardiopulmonary exercise testing in chronic heart failure due to left ventricular dysfunction: recommendations for performance and interpretation Part II: How to perform cardiopulmonary exercise testing in chronic heart failure. *Eur J Cardiovasc Prev Rehabil* 2006 June;13(3):300-11.

(69) Abidov A, Rozanski A, Hachamovitch R et al. Prognostic significance of dyspnea in patients referred for cardiac stress testing. *N Engl J Med* 2005 November 3;353(18):1889-98.

(70) Weiner DA, McCabe C, Hueter DC, Ryan TJ, Hood WB, Jr. The predictive value of anginal chest pain as an indicator of coronary disease during exercise testing. *Am Heart J* 1978 October;96(4):458-62.

(71) Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH, Jr., Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* 1991 March;83(3):778-86.

(72) Myers J. Information from Ventilatory Gas Exchange Data. In: Washburn R, editor. *Essentials of Cardiopulmonary Exercise Testing*.Champaign: Human Kinetics; 1996. p. 83-108.

(73) Guazzi M, Reina G, Tumminello G, Guazzi MD. Exercise ventilation inefficiency and cardiovascular mortality in heart failure: the critical independent prognostic value of the arterial CO2 partial pressure. *European Heart Journal* 2004 December 14;ehi060.

(74)   Tanabe Y, Hosaka Y, Ito M, Ito E, Suzuki K. Significance of end-tidal P(CO(2)) response to exercise and its relation to functional capacity in patients with chronic heart failure. *Chest* 2001 March;119(3):811-7.

(75)   Matsumoto A, Itoh H, Eto Y et al. End-tidal CO2 pressure decreases during exercise in cardiac patients: association with severity of heart failure and cardiac output reserve. *J Am Coll Cardiol* 2000 July;36(1):242-9.

(76)   Ponikowski P, Francis DP, Piepoli MF et al. Enhanced ventilatory response to exercise in patients with chronic heart failure and preserved exercise tolerance: marker of abnormal cardiorespiratory reflex control and predictor of poor prognosis. *Circulation* 2001 February 20;103(7):967-72.

(77)   Ponikowski PP, Chua TP, Francis DP, Capucci A, Coats AJS, Piepoli MF. Muscle Ergoreceptor Overactivity Reflects Deterioration in Clinical Status and Cardiorespiratory Reflex Control in Chronic Heart Failure. *Circulation* 2001 November 6;104(19):2324-30.

(78)   Wada O, Asanoi H, Miyagi K et al. Importance of abnormal lung perfusion in excessive exercise ventilation in chronic heart failure. *Am Heart J* 1993 March;125(3):790-8.

(79)   Reindl I, Wernecke KD, Opitz C et al. Impaired ventilatory efficiency in chronic heart failure: possible role of pulmonary vasoconstriction. *Am Heart J* 1998 November;136(5):778-85.

(80)   Baba R, Nagashima M, Goto M et al. Oxygen intake efficiency slope: a new index of cardiorespiratory functional reserve derived from the relationship between oxygen consumption and minute ventilation during incremental exercise. *Nagoya J Med Sci* 1996 March;59(1-2):55-62.

(81)   Defoor J, Schepers D, Reybrouck T, Fagard R, Vanhees L. Oxygen uptake efficiency slope in coronary artery disease: clinical use and response to training. *Int J Sports Med* 2006 September;27(9):730-7.

(82)   Arena R, Myers J, Guazzi M et al. The minute ventilation/carbon dioxide production slope prognostically outperforms the oxygen uptake efficiency slope. Journal of the American College of Cardiology In press. 2006.
        Ref Type: Abstract

(83)   Bluemke DA, Achenbach S, Budoff M et al. Noninvasive coronary artery imaging: magnetic resonance angiography and multidetector computed tomography angiography: a scientific statement from the american heart association committee on cardiovascular imaging and intervention of the council on cardiovascular radiology and intervention, and the councils on clinical cardiology and cardiovascular disease in the young. *Circulation* 2008 July 29;118(5):586-606.

(84) Noto TJ, Jr., Johnson LW, Krone R et al. Cardiac catheterization 1990: a report of the Registry of the Society for Cardiac Angiography and Interventions (SCA&I). *Cathet Cardiovasc Diagn* 1991 October;24(2):75-83.

(85) Rodgers GP, Ayanian JZ, Balady G et al. American College of Cardiology/American Heart Association Clinical Competence Statement on Stress Testing : A Report of the American College of Cardiology/American Heart Association/American College of Physicians-American Society of Internal Medicine Task Force on Clinical Competence. *Circulation* 2000 October 3;102(14):1726-38.

(86) Klocke FJ, Baird MG, Lorell BH et al. ACC/AHA/ASNC Guidelines for the Clinical Use of Cardiac Radionuclide Imaging--Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). *Circulation* 2003 September 16;108(11):1404-18.

(87) Iskandrian AS, Heo J, Kong B, Lyons E. Effect of exercise level on the ability of thallium-201 tomographic imaging in detecting coronary artery disease: analysis of 461 patients. *J Am Coll Cardiol* 1989 November 15;14(6):1477-86.

(88) Cheitlin MD, Armstrong WF, Aurigemma GP et al. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). *Circulation* 2003 September 2;108(9):1146-62.

(89) Marwick TH, Nemec JJ, Pashkow FJ, Stewart WJ, Salcedo EE. Accuracy and limitations of exercise echocardiography in a routine clinical setting. *J Am Coll Cardiol* 1992 January;19(1):74-81.

(90) Quinones MA, Verani MS, Haichin RM, Mahmarian JJ, Suarez J, Zoghbi WA. Exercise echocardiography versus 201Tl single-photon emission computed tomography in evaluation of coronary artery disease. Analysis of 292 patients. *Circulation* 1992 March;85(3):1026-31.

(91) Hsi WL, Wong PL, Lai JS. Submaximal oxygen pulse divided by body weight during incremental exercise test. *Am J Phys Med Rehabil* 1997 July;76(4):297-303.

(92) Klainman E, Fink G, Lebzelter J, Krelbaumm T, Kramer MR. The relationship between left ventricular function assessed by multigated radionuclide test and cardiopulmonary exercise test in patients with ischemic heart disease. *Chest* 2002 March;121(3):841-5.

(93) Piepoli MF, Corra U, Agostoni PG et al. Statement on cardiopulmonary exercise testing in chronic heart failure due to left ventricular dysfunction: recommendations for performance and interpretation. Part I: definition of cardiopulmonary exercise testing parameters for appropriate use in chronic heart failure. *Eur J Cardiovasc Prev Rehabil* 2006 April;13(2):150-64.

(94) Lloyd-Jones D, Adams RJ, Brown TM et al. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. *Circulation* 2010 February 23;121(7):e46-e215.

(95) Pinkstaff S, Peberdy MA, Fabiato A, Finucane S, Arena R. The clinical utility of cardiopulmonary exercise testing in suspected or confirmed myocardial ischemia. American Journal of Lifestyle Medicine. In press 2009.

(96) Hunt SA, Baker DW, Chin MH et al. ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult: Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). *Circulation* 2001 December 11;104(24):2996-3007.

(97) Arena R, Lavie CJ, Milani RV, Myers J, Guazzi M. Cardiopulmonary Exercise Testing in Patients with Pulmonary Hypertension: An Evidence-Based Review. Journal of Heart and Lung Transplantation. In press 2009.

(98) Christopher JR, Pothier CE, Blackstone EH, Lauer MS. Prognostic importance of presenting symptoms in patients undergoing exercise testing for evaluation of known or suspected coronary disease. *Am J Med* 2004 September 15;117(6):380-9.

(99) Morise AP, Jalisi F. Evaluation of pretest and exercise test scores to assess all-cause mortality in unselected patients presenting for exercise testing with symptoms of suspected coronary artery disease. *J Am Coll Cardiol* 2003 September 3;42(5):842-50.

(100) Kailasnath P, Sinusas AJ. Technetium-99m-labeled myocardial perfusion agents: Are they better than thallium-201? *Cardiol Rev* 2001 May;9(3):160-72.

(101) Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *Am Heart J* 1973 April;85(4):546-62.

(102) Myers J, Arena R, Franklin B et al. Recommendations for clinical exercise laboratories: a scientific statement from the american heart association. *Circulation* 2009 June 23;119(24):3144-61.

(103) Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982;14(5):377-81.

(104) Ho SW, McComish MJ, Taylor RR. Effect of beta-adrenergic blockade on the results of exercise testing related to the extent of coronary artery disease. *Am J Cardiol* 1985 February 1;55(4):258-62.

(105) Baba R, Nagashima M, Goto M et al. Oxygen uptake efficiency slope: a new index of cardiorespiratory functional reserve derived from the relation between oxygen uptake and minute ventilation during incremental exercise. *J Am Coll Cardiol* 1996 November 15;28(6):1567-72.

(106) Arena R, Arrowood JA, Fei DY, Helm S, Kraft KA. Maximal aerobic capacity and the oxygen uptake efficiency slope as predictors of large artery stiffness in apparently healthy subjects. *J Cardiopulm Rehabil Prev* 2009 July;29(4):248-54.

(107) Hollenberg M, Tager IB. Oxygen uptake efficiency slope: an index of exercise performance and cardiopulmonary reserve requiring only submaximal exercise. *J Am Coll Cardiol* 2000 July;36(1):194-201.

(108) Baba R, Tsuyuki K, Yano H, Ninomiya K, Ebine K. Robustness of the oxygen uptake efficiency slope to exercise intensity in patients with coronary artery disease. *Nagoya J Med Sci* 2010 February;72(1-2):83-9.

(109) Baba R, Tsuyuki K, Kimura Y et al. Oxygen uptake efficiency slope as a useful measure of cardiorespiratory functional reserve in adult cardiac patients. *Eur J Appl Physiol Occup Physiol* 1999 October;80(5):397-401.

(110) Baba R, Nagashima M, Nagano Y, Ikoma M, Nishibata K. Role of the oxygen uptake efficiency slope in evaluating exercise tolerance. *Arch Dis Child* 1999 July;81(1):73-5.

(111) Van LC, Van d, V, De SJ et al. Prospective evaluation of the oxygen uptake efficiency slope as a submaximal predictor of peak oxygen uptake in aged patients with ischemic heart disease. *Am Heart J* 2006 August;152(2):297-15.

(112) Baba R, Tsuyuki K, Yano H, Ninomiya K, Ebine K. Robustness of the oxygen uptake efficiency slope to exercise intensity in patients with coronary artery disease. *Nagoya J Med Sci* 2010 February;72(1-2):83-9.

(113) O'Keefe-McCarthy S. Women's experiences of cardiac pain: a review of the literature. *Can J Cardiovasc Nurs* 2008;18(3):18-25.

(114) Shaw LJ, Merz CN, Pepine CJ 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* 2006 August 29;114(9):894-904.

(115) Shaw LJ, Bugiardini R, Merz CN. Women and ischemic heart disease: evolving knowledge. *J Am Coll Cardiol* 2009 October 20;54(17):1561-75.

(116) Makaryus AN, Shaw LJ, Mieres JH. Diagnostic strategies for heart disease in women: an update on imaging techniques for optimal management. *Cardiol Rev* 2007 November;15(6):279-87.

(117) Taillefer R, DePuey EG, Udelson JE, Beller GA, Latour Y, Reeves F. Comparative diagnostic accuracy of Tl-201 and Tc-99m sestamibi SPECT imaging (perfusion and ECG-gated SPECT) in detecting coronary artery disease in women. *J Am Coll Cardiol* 1997 January;29(1):69-77.

(118) Buchthal SD, den Hollander JA, Merz CN et al. Abnormal myocardial phosphorus-31 nuclear magnetic resonance spectroscopy in women with chest pain but normal coronary angiograms. *N Engl J Med* 2000 March 23;342(12):829-35.

(119) Panting JR, Gatehouse PD, Yang GZ et al. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *N Engl J Med* 2002 June 20;346(25):1948-53.

(120) Panting JR, Gatehouse PD, Yang GZ et al. Abnormal subendocardial perfusion in cardiac syndrome X detected by cardiovascular magnetic resonance imaging. *N Engl J Med* 2002 June 20;346(25):1948-53.

(121) Delcour KS, Khaja A, Chockalingam A, Kuppuswamy S, Dresser T. Outcomes in patients with abnormal myocardial perfusion imaging and normal coronary angiogram. *Angiology* 2009 June;60(3):318-21.

(122) Bugiardini R. Normal coronary arteries: clinical implications and further classification. *Herz* 2005 February;30(1):3-7.

(123) Erbel R, Ge J, Bockisch A et al. Value of intracoronary ultrasound and Doppler in the differentiation of angiographically normal coronary arteries: a prospective study in patients with angina pectoris. *Eur Heart J* 1996 June;17(6):880-9.

(124) Wiedermann JG, Schwartz A, Apfelbaum M. Anatomic and physiologic heterogeneity in patients with syndrome X: an intravascular ultrasound study. *J Am Coll Cardiol* 1995 May;25(6):1310-7.

(125) Mark DB, Hlatky MA, Harrell FE, Jr., Lee KL, Califf RM, Pryor DB. Exercise treadmill score for predicting prognosis in coronary artery disease. *Ann Intern Med* 1987 June;106(6):793-800.

(126) Shaw LJ, Peterson ED, Shaw LK et al. Use of a prognostic treadmill score in identifying diagnostic coronary disease subgroups. *Circulation* 1998 October 20;98(16):1622-30.

(127) Stuart RJ, Jr., Ellestad MH. National survey of exercise stress testing facilities. *Chest* 1980 January;77(1):94-7.

(128) Myers J, Voodi L, Umann T, Froelicher VF. A survey of exercise testing: methods, utilization, interpretation, and safety in the VAHCS. *J Cardiopulm Rehabil* 2000 July;20(4):251-8.

(129) Kodama S, Saito K, Tanaka S et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA* 2009 May 20;301(19):2024-35.

(130) Milani RV, Lavie CJ, Spiva H. Limitations of estimating metabolic equivalents in exercise assessment in patients with coronary artery disease. *Am J Cardiol* 1995 May 1;75(14):940-2.

(131) Froelicher VF, Jr., Thompson AJ, Jr., Davis G, Stewart AJ, Triebwasser JH. Prediction of maximal oxygen consumption. Comparison of the Bruce and Balke treadmill protocols. *Chest* 1975 September;68(3):331-6.

(132) Myers J, Buchanan N, Walsh D et al. Comparison of the ramp versus standard exercise protocols. *J Am Coll Cardiol* 1991 May;17(6):1334-42.

(133) Wasserman K, Hansen JE, Sue DY. *Principles of Exercise Testing and Interpretation*. 2 ed. Philadelphia: Lea and Febiger; 1994.

(134) Armstrong L, Balady G, Berry M et al. *ACSM's Guidelines for Exercise Testing and Prescription*. 7th ed. Philadelphia: Lippincott Williams and Wilkins; 2006.

(135) Redwood DR, Rosing DR, Goldstein RE, Beiser GD, Epstein SE. Importance of the design of an exercise protocol in the evaluation of patients with angina pectoris. *Circulation* 1971 May;43(5):618-28.

(136) Myers J, Walsh D, Buchanan N, Froelicher VF. Can maximal cardiopulmonary capacity be recognized by a plateau in oxygen uptake? *Chest* 1989 December;96(6):1312-6.

(137) Arena R, Myers J, Williams MA et al. Assessment of functional capacity in clinical and research settings: a scientific statement from the American Heart Association Committee on Exercise, Rehabilitation, and Prevention of the Council on Clinical Cardiology and the Council on Cardiovascular Nursing. *Circulation* 2007 July 17;116(3):329-43.

(138) Manfre MJ, Yu GH, Varma AA, Mallis GI, Kearney K, Karageorgis MA. The effect of limited handrail support on total treadmill time and the prediction of VO2 max. *Clin Cardiol* 1994 August;17(8):445-50.

(139) Berling J, Foster C, Gibson M, Doberstein S, Porcari J. The effect of handrail support on oxygen uptake during steady-state treadmill exercise. *J Cardiopulm Rehabil* 2006 November;26(6):391-4.

(140) McConnell TR, Clark B. Prediction of Maximal Oxygen Consumption During Handrail Supported Treadmill Exercise. *Journal of Cardiopulmonary Rehabilitation* 1987 January 1;7:324-31.

(141) Shaw LJ, Peterson ED, Shaw LK et al. Use of a prognostic treadmill score in identifying diagnostic coronary disease subgroups. *Circulation* 1998 October 20;98(16):1622-30.

(142) Pate RR, Pratt M, Blair SN et al. Physical activity and public health. A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA* 1995 February 1;273(5):402-7.

(143) Delcour KS, Khaja A, Chockalingam A, Kuppuswamy S, Dresser T. Outcomes in patients with abnormal myocardial perfusion imaging and normal coronary angiogram. *Angiology* 2009 June;60(3):318-21.

(144) Bugiardini R. Normal coronary arteries: clinical implications and further classification. *Herz* 2005 February;30(1):3-7.

(145) Erbel R, Ge J, Bockisch A et al. Value of intracoronary ultrasound and Doppler in the differentiation of angiographically normal coronary arteries: a prospective study in patients with angina pectoris. *Eur Heart J* 1996 June;17(6):880-9.

(146) Wiedermann JG, Schwartz A, Apfelbaum M. Anatomic and physiologic heterogeneity in patients with syndrome X: an intravascular ultrasound study. *J Am Coll Cardiol* 1995 May;25(6):1310-7.

(147) Myers J, Froelicher VF. Optimizing the exercise test for pharmacological investigations. *Circulation* 1990 November;82(5):1839-46.