Exercise-Induced Myocardial Ischemia Detected by Cardiopulmonary Exercise Testing

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Cardiopulmonary exercise testing (CPET) is a well-accepted physiologic evaluation technique in patients diagnosed with heart failure and in patients presenting with unexplained dyspnea on exertion. Several variables obtained during CPET, including oxygen consumption relative to heart rate and work rate provide consistent, quantitative patterns of abnormal physiologic responses to graded exercise when left ventricular dysfunction is caused by myocardial ischemia. This concept report describes both the methodology and clinical application of CPET associated with myocardial ischemia. Initial evidence indicates left ventricular dysfunction induced by myocardial ischemia may be accurately detected by an abnormal CPET response. CPET testing may complement current noninvasive testing modalities that elicit inducible ischemia. It provides a physiologic quantification of the work rate, heart rate, and O_2 uptake at which myocardial ischemia develops. In conclusion, adding CPET with gas exchange measurements is likely to be of value in diagnosing and quantifying both overt and occult myocardial ischemia and its reversibility with treatment. © 2009 Elsevier Inc. (Am J Cardiol 2009;103:615–619)

Compared with traditional imaging modalities, cardiopulmonary exercise testing (CPET) provides a unique approach to assess exercise-induced ischemia. Accurate detection of myocardial ischemia by CPET relies on the physiologic principle that myocardial contractility depends on the regeneration of high energy phosphate compounds, such as adenosine triphosphate, in all regions of the myocardium. The adenosine triphosphate must be regenerated during myocardial contraction and/or relaxation by oxidative metabolism (O_2-releasing energy from energy supplying substrate). The myocardium becomes ischemic when the work rate is sufficiently high to induce the state of O_2 supply - O_2 demand imbalance. Measurement of CPET variables in real time, therefore, enables the potential for detection of ischemia-induced left ventricular (LV) dysfunction in response to increasing work rate. Hence, patients with or without chest pain or dyspnea can demonstrate physiological responses to exercise characteristic of abrupt reductions in stroke volume. The purpose of this concept report is to illustrate the potential value of CPET in detecting both macro- and microvascular coronary artery disease (CAD).

Methods

Key CPET variables and testing protocol: Thorough description of the numerous variables that can be derived from CPET have been previously described.[1–3] The change in the O_2-pulse related to increase in work rate and the exercise heart rate (HR) as related to increasing oxygen uptake (VO_2) appear to be key CPET responses in the diagnosis of CAD. The O_2-pulse, calculated as O_2 uptake divided by HR (VO_2/HR) equals stroke volume × arteriovenous O_2 difference. The latter is reproducible at the anerobic threshold and peak VO_2 if the hemoglobin and oxyhemoglobin saturation are taken into account. Therefore, the stroke volume can be estimated at these points of increasing work rate exercise if gas exchange is simultaneously measured.[4,5]

Symptom-limited CPET was performed on an electromagnetically-braked cycle ergometer (Ergoselect 100P, Ergoline GmbH, Bitz, Germany) using a customized linear ramp protocol designed to elicit fatigue within 8 to 12 minutes of exercise initiation. Exercise of this duration has been shown to produce the highest peak VO_2 values.[6,7] The protocol consisted of 3 minutes of rest, 3 minutes of pedaling with no load, followed by pedaling against a customized continuously increasing work rate in a ramp pattern to tolerance.[8] The ramp work rate was selected based on the patient's predicted peak VO_2, recognizing that VO_2 normally increases at a rate of 10 ml/min/watt using previously validated methodology.[8]

During CPET, a 12-lead electrocardiogram (Quark C12, Cosmed Srl, Italy) and a pulse oximeter with a finger probe

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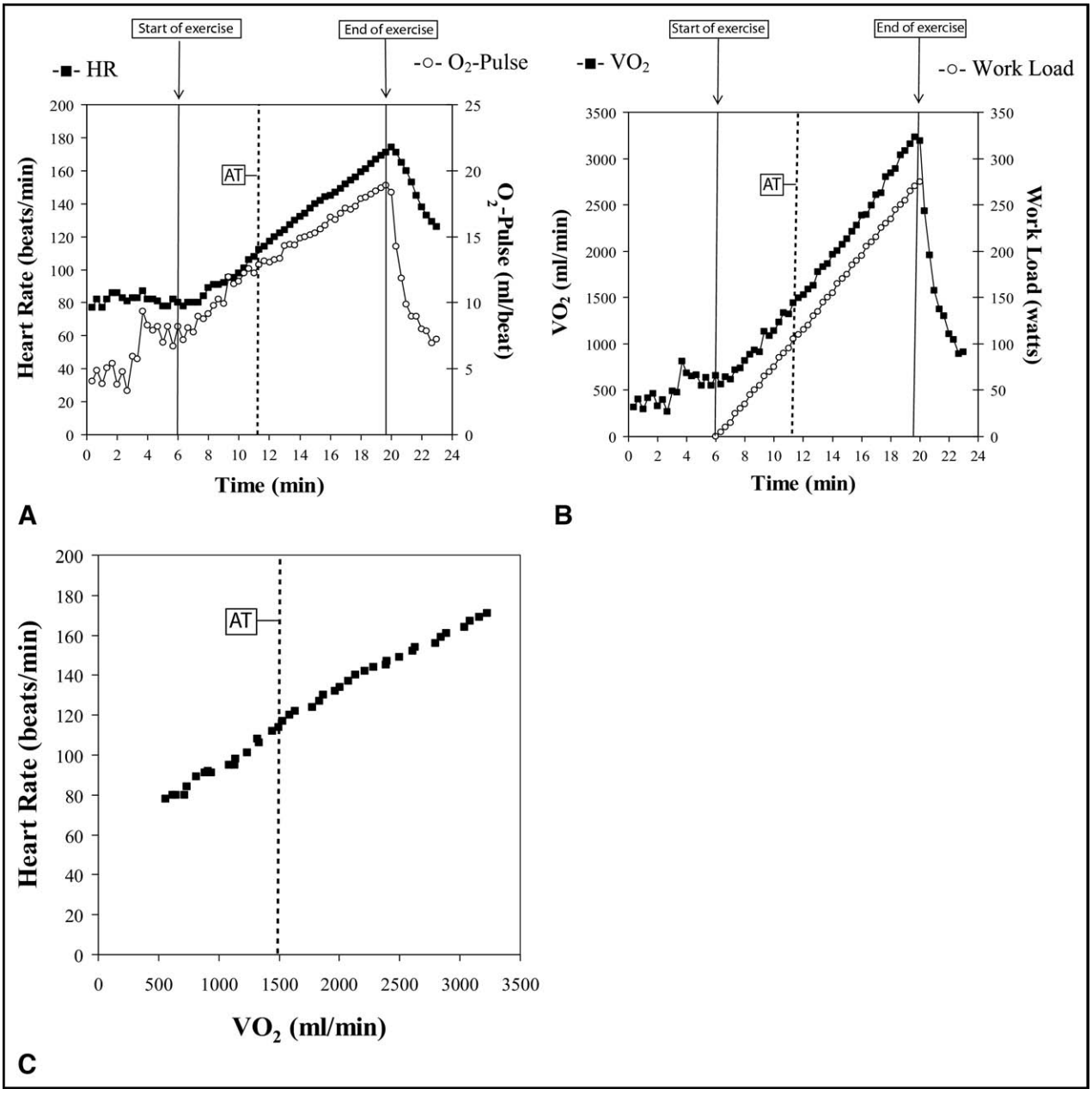

Figure 1. AT = Anerobic threshold, determined by the V-slope method; VO_2 = Oxygen uptake in ml/min; HR = Heart rate in beats/ minute; O_2-Pulse = Oxygen pulse, oxygen uptake in ml/min divided by HR in beats/min.

(Model 100 Pulse Oximeter, Mediaid, Inc., Cerritos, California) were continuously monitored, and blood pressure was manually assessed every 2 minutes with a cuff sphygmomanometer. A disposable face mask with a 50 to 80 ml dead space (Clear Comfort Air Cushion Face Mask, Hudson RCI, Durham, North Carolina) was used to collect expired air throughout the test. Minute ventilation, carbon dioxide output, and oxygen uptake (VO_2) were recorded with a breath-by-breath measurement system (Cosmed Quark PFT 4 Ergo, Cosmed Srl, Italy). The flow meter and gas analyzers were calibrated before each test according to the manufacturer's instructions.

Peak VO_2 was recorded as the highest consecutive 30-second averaged value during the last minute of exercise or early recovery. The anerobic threshold was determined by the V-slope method.[9] All responses were monitored throughout rest, exercise, and recovery and graphically displayed.

Results

Illustration of a normal and abnormal response:

NORMAL CPET RESPONSE: The normal O_2-pulse versus time, $\Delta VO_2/\Delta$work rate, and HR versus O_2 uptake responses to a progressively increasing work rate during exercise are illustrated in Figure 1. The test data are from a 49-year-old asymptomatic firefighter who was enrolled in a fitness and genetic study of this population. His medical

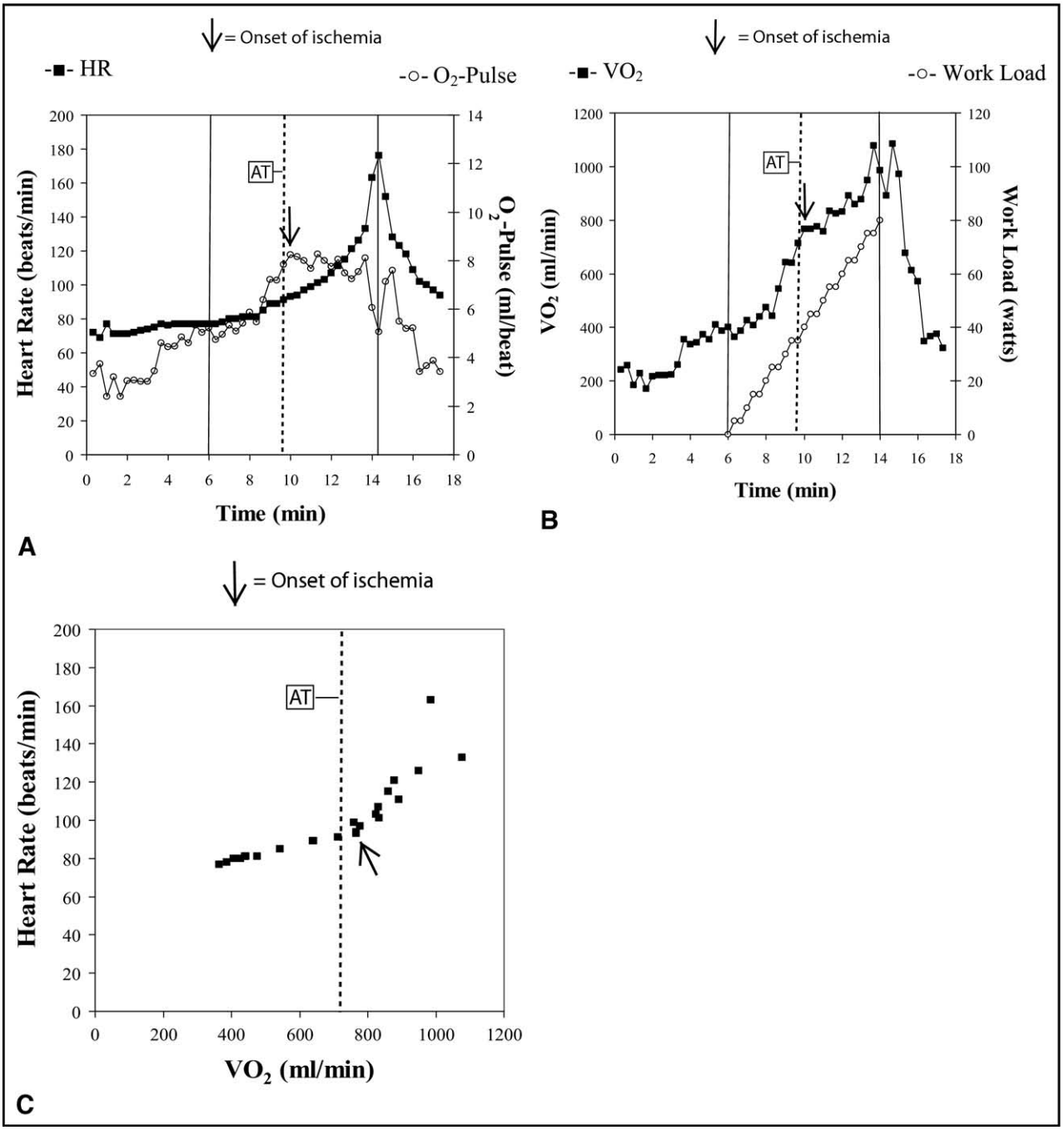

Figure 2. AT = Anerobic threshold, determined by the V-slope method; VO_2 = Oxygen uptake in ml/min; HR = Heart rate in beats/ minute; O_2-Pulse = Oxygen pulse, oxygen uptake in ml/min divided by HR in beats/min.

history was only significant for hypothyroidism; however, the subject was euthyroid at the time of testing. He never smoked, there was no family history of heart disease, and he exercised 3 to 4 times a week. Physical exam and at rest electrocardiogram were normal.

The subject tolerated the test without complications and put forth a good effort. He achieved a respiratory exchange ratio (carbon dioxide output/oxygen uptake) of 1.13 at peak exercise indicating significant lactic acidosis and adequate cardiovascular stress. The patient terminated exercise because of leg fatigue. Peak HR was 101% of age-predicted maximum. Blood pressures at rest and at peak exercise were 124/80 mm Hg and 220/100 mm Hg, respectively. The subject achieved a peak VO_2 of 30.3 $mlO_2 \cdot kg^{-1} \cdot min^{-1}$, which is 113% of predicted for age, height, weight, and gender (predicted peak VO_2 $\geq$85% is considered to be normal exercise capacity).[8] The VO_2 at the anerobic threshold of 14.0 $mlO_2 \cdot kg^{-1} \cdot min^{-1}$ was likewise within normal limits. O_2-pulse increased in a normal linear manner to the predicted peak value; the VO_2 increased in a linear manner relative to work load to peak predicted value, and HR response versus VO_2 was also linear from rest to peak

exercise (Figure 1). The electrocardiogram revealed isolated premature ventricular beats near peak exercise with no demonstrable ST changes.

ABNORMAL CPET RESPONSE: Characteristic CPET findings related to exercise-induced ischemia were evident in a 68-year-old woman with a 50 pack-year smoking history, hypertension, and dyslipidemia who was referred for a CPET as part of preoperative evaluation. The patient reported claudication with abnormal noninvasive vascular studies and was scheduled for an elective endovascular peripheral arterial disease procedure. Medications included valsartan, hydrochlorothiazide, rosuvastatin, ezetimibe, niacin, and venlafaxine. Her at rest electrocardiogram showed normal sinus rhythm with no other abnormalities.

The subject tolerated the test without complications and put forth a good effort. She achieved a respiratory exchange ratio of 1.4 at peak exercise indicative of development of a significant lactic acidosis. The patient terminated exercise because of leg pain. Peak HR was 88% of her age-predicted maximum. Blood pressures at rest and at peak exercise were 148/82 mm Hg and 218/96 mm Hg, respectively. She achieved a peak VO_2 of 17.2 $mlO_2 \cdot kg^{-1} \cdot min^{-1}$, which is 89% of predicted. Her VO_2 at the anerobic threshold of 12.3 $mlO_2 \cdot kg^{-1} \cdot min^{-1}$ was likewise within normal limits. However, the patient developed gas exchange evidence of LV dysfunction at a HR of 93 beats/min as indicated by a reduced peak O_2-pulse that gradually decreased with increasing work rate, an abrupt decrease in $\Delta VO_2/\Delta$work rate slope, and a steepening of the HR-VO_2 uptake slope (Figure 2). These concurrent changes are characteristic of exercise-induced decreasing stroke volume resulting from myocardial dysfunction caused by ischemia. The electrocardiogram revealed isolated premature ventricular beats near peak exercise with no demonstrable ST-segment changes.

On the basis of the abnormal physiologic findings, the patient underwent coronary angiography which revealed a >95% critical stenosis of the right coronary artery. This was treated with intracoronary stent placement.

Discussion

During a progressive, ramped exercise test designed to elicit maximal exertion, cardiac output increases through a synergistic augmentation of both stroke volume and HR as external work rate increases. Under normal physiologic conditions, these cardiovascular adaptations will result in a progressively increasing O_2-pulse, a linear increase in VO_2 versus work rate with a slope of approximately 10 ml/min/watt and a linear increase in HR versus VO_2 to normal peak values. If a patient has obstructive CAD and the myocardium does not receive sufficient O_2 to maintain normal myocardial contraction, the myocardial segments that are rendered ischemic will exhibit abnormal contraction patterns or myocardial dyssynergy (hypokinesis, akinesis, or dyskinesis), which can range from mild to severe depending on the extent and magnitude of ischemia. Thus, when myocardial perfusion is reduced producing an O_2 supply - O_2 demand imbalance, whether from epicardial coronary disease or impaired coronary flow reserve involving the arteriolar resistance vessels, reversible LV dysfunction will result. Thus, CPET quantifies the ischemic work rate threshold. Exceeding the ischemic work rate threshold causes stroke volume to decrease while HR increases faster relative to VO_2 in partial, but incomplete, compensation. Paralleling the failure to maintain a cardiac output increase appropriate for a given increase in work rate is a characteristic flattening or reduction of increase in $\Delta VO_2/\Delta$work rate, and a decline or lack of progressive increase in O_2-pulse, with a concomitant steepening of the slope of HR-VO_2 uptake relation (Figure 2). Because the degree of LV dysfunction detected by CPET is directly proportional to the extent of underlying ischemic burden, severe CAD, such as triple vessel disease, is the most likely form of CAD to be detected by CPET.[10]

Previous research in this area has focused on the utility of CPET in detecting macrovascular CAD.[11] It is now recognized that microvascular CAD, particularly in women, is a significant health care concern.[12,13] To better detect this condition, new methods of evaluation must be implemented.[14] Peix et al[15] previously demonstrated that postmenopausal women with normal coronary angiograms but diagnosed with microvascular CAD frequently developed LV dysfunction during exercise testing. Subjects with either macro- or microvascular CAD may demonstrate a similar CPET response, although nuclear imaging and cardiac catheterization findings may be different. Given the potential for CPET to accurately detect LV dysfunction in a noninvasive and cost-effective manner, implementation of this assessment technique in the evaluation of suspected microvascular disease may be clinically advantageous, prompting more appropriate follow-up tests with a high proclivity for microvascular CAD detection, such as magnetic resonance imaging[16] and perhaps phosphorus-31 nuclear magnetic resonance spectroscopy.[17]

Concomitant gas exchange analysis provides valuable physiologic information that precisely demarcates the HR, VO_2, and work-rate at which ischemic LV dysfunction develops. The characteristic changes in O_2-pulse, $\Delta VO_2/\Delta$work rate, and pattern of HR-VO_2 response may, therefore, also be useful in assessing the response to a given therapeutic intervention in a serial fashion, particularly as treatments for myocardial ischemia emerge. Recent evidence that the anatomic definition of angiographic CAD and subsequent percutaneous coronary intervention does not inevitably lead to improved outcomes reinforces the need for more precision in characterizing the functional consequences of myocardial ischemia in patients with macrovascular CAD for whom invasive strategies are being considered.[18] Serial CPET testing has been used to demonstrate normalization of LV function after revascularization in a patient with isolated right coronary artery (RCA) disease similar to the abnormal response described.[19]

The use of expired gas analysis is not common practice in the contemporary clinical exercise laboratory. Future research should continue in this area to more quantifiably determine the value of CPET in diagnosing both macro- and microvascular CAD, assessing responses to therapy, and predicting prognosis in CAD. Although initial findings are compelling, compilation of additional clinical information and physician education are needed to gain widespread clinical acceptance.

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