

The Utility of Cardiopulmonary Exercise Testing to Detect and Track Early-Stage Ischemic Heart Disease

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Evidence demonstrating the potential value of noninvasive cardiopulmonary exercise testing (CPET) to accurately detect exercise-induced myocardial ischemia is emerging. This case-based concept report describes CPET abnormalities in an asymptomatic at-risk man with suspected early-stage ischemic heart disease. When CPET was repeated 1 year after baseline assessment, his cardiovascular function had worsened, and an anti-atherosclerotic regimen was initiated. When the patient was retested after 3.3 years, the diminished left ventricular function had reversed with pharmacotherapy directed at decreasing cardiovascular events in patients with coronary artery disease. Thus, in addition to identifying appropriate patients in need of escalating therapy for atherosclerosis, CPET was useful in monitoring progression and reversal of abnormalities of the coronary circulation in a safe and cost-effective manner without the use of radiation. Serial CPET parameters may be useful to track changes marking the progression and/or regression of the underlying global ischemic burden.

Mayo Clin Proc. 2010;85(10):928-932

AT = anaerobic threshold; BP = blood pressure; CAD = coronary artery disease; CPET = cardiopulmonary exercise testing; HDL-C = high-density lipoprotein cholesterol; HR = heart rate; IT = ischemic threshold; LDL-C = low-density lipoprotein cholesterol; LV = left ventricular; O₂ = oxygen; RER = respiratory exchange ratio; $\dot{V}O_2$ = oxygen uptake; WR = work rate

A more effective approach is needed not only to identify asymptomatic at-risk individuals with early-stage ischemic heart disease but also to assess the efficacy of chronic disease-modifying therapies before the occurrence of the first cardiovascular event. The myocardium typically becomes ischemic first during physical exertion. Therefore, left ventricular (LV) dysfunction during exercise provides the earliest opportunity to detect the development of a physiologically, and hence clinically, important ischemic burden. The physiologic basis for applying gas exchange measurements to detect myocardial ischemia rests on the assumption that this is a sensitive tool in depicting the decline in LV function brought about by ischemia. Specifically, stroke volume decreases at workloads above the ischemic threshold (IT), reducing the rate of increase in oxygen uptake ($\dot{V}O_2$) relative to the increase in work rate (WR), with a concomitant steepening of the heart rate (HR) response as a compensatory mechanism.¹

In populations subject to coronary artery disease (CAD), serial cardiopulmonary exercise testing (CPET) may prove to be a valuable tool in detecting exercise-induced myocardial dysfunction and its progression and/or regression,

regardless of mechanism. Exercise capacity (or cardiorespiratory fitness) is a powerful predictor of all-cause mortality.² This premise appears to hold true in asymptomatic healthy individuals as well as patient populations with chronic disease.³ If the underlying cardiac disease process worsens, so do parameters of oxygen (O₂) transport, exercise capacity, and prognosis. This case study describes the CPET response of a patient with suspected early-stage ischemic heart disease before and after receiving disease-modifying anti-ischemic therapies shown to decrease cardiovascular events in the CAD population.

CASE REPORT

BASELINE ASSESSMENT (TEST 1)

An asymptomatic 36-year-old man of South Asian ancestry had a strong family history of premature CAD, with a primary cardiovascular event occurring in most male relatives in their fourth or fifth decade of life. He had never smoked and did not exercise regularly. He was not taking any medications and had no other history of cardiac problems. His body mass index (calculated as the weight in kilograms divided by height in meters squared) was 27.8.

The patient underwent his first CPET in July 2005 on a cycle ergometer, performing a 20-W ramp protocol⁴ and stopping because of leg fatigue. He reached a peak exercise respiratory exchange ratio (RER) of 1.39, a peak HR of 91% of the age-predicted value, and a peak $\dot{V}O_2$ of 25 mL/kg/min (70% of predicted).⁴ His resting blood pres-

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sure (BP) was 102/64 mm Hg, and BP at peak exercise was 198/74 mm Hg. No ST-segment changes or arrhythmias occurred during exercise. His $\dot{V}O_2$ kinetics became grossly abnormal shortly above the anaerobic threshold (AT). At a WR of 100 W, exercise-induced myocardial dysfunction was reflected by the abrupt change in $\dot{V}O_2$ as a function of increasing WR ($\Delta\dot{V}O_2/\Delta WR$), peaking of O_2 pulse ($\dot{V}O_2/HR$) followed by a decreasing trend toward the end of exercise and a concomitant steepening of HR response as a function of increasing cardiac output (HR vs $\dot{V}O_2$), all of which diverted from their expected normal linear trajectory (Figure, test 1). The increasing O_2 pulse is a product of stroke volume and arteriovenous O_2 difference during exercise (Fick equation). A flat or slightly decreasing O_2 pulse indicates a decrease in stroke volume because peripheral tissue extraction (arteriovenous O_2 difference) normally increases while WR and O_2 uptake are increasing. $\Delta\dot{V}O_2/\Delta WR$ (reflecting the product of cardiac output \times arteriovenous O_2 difference relative to workload performed) only becomes shallower above the AT when cardiac output is insufficient to keep up with increasing workload.

The patient was seen by his primary care physician for further evaluation and was found to have substantial dyslipidemia. His lipid values were as follows: total cholesterol, 249 mg/dL; low-density lipoprotein cholesterol (LDL-C), 180 mg/dL; triglycerides, 152 mg/dL; and high-density lipoprotein cholesterol (HDL-C), 36 mg/dL. He also had elevated lipoprotein(a) (12.0 mg/dL) and elevated C-reactive protein levels. (To convert total cholesterol, LDL-C, and HDL-C values to mmol/L, multiply by 0.0259; to convert triglyceride value to mmol/L, multiply by 0.0113; and to convert lipoprotein(a) value to $\mu\text{mol/L}$, multiply by 0.0357.) He had no evidence of hypertension or diabetes. During the next 12 months, he attempted to control his lipid levels primarily through diet and made no substantial change in exercise habits.

TEST 2

The patient underwent a second CPET about 1 year later to reassess his cardiovascular status. He performed the same 20-W ramp protocol and stopped exercising because of leg fatigue. He reached a peak RER of 1.45, a peak HR of 85% of the age-predicted value, and a peak $\dot{V}O_2$ of 23 mL/kg/min (66% of predicted). His resting BP was 110/82 mm Hg, and his BP at peak exercise was 190/80 mm Hg. As with test 1, his $\dot{V}O_2$ kinetics became grossly abnormal shortly above the AT. This time, the break from increasing of the $\Delta\dot{V}O_2/\Delta WR$, O_2 pulse, and HR vs $\dot{V}O_2$ response was noted at a WR of 75 W. The Figure (test 2) illustrates the response patterns. No ST-segment changes or arrhythmias occurred during the second test. The worsening changes in test 2 compared with test 1 are significant in that the onset of the abnormality reflect-

ing LV dysfunction occurred at a lower WR (75 W vs 100 W) and earlier during exercise (~10-minute mark vs ~11-minute mark), and the contours of the response curves are more abnormal, suggesting greater LV dysfunction during exercise. Peak $\dot{V}O_2$ (a noninvasive surrogate of peak cardiac output) was slightly decreased from 70% to 66% (variability of CPET measurements in the laboratory where the studies were performed is 3% to 5%, as determined using biological controls). The O_2 pulse at peak exercise (a noninvasive surrogate of stroke volume at peak exercise) was also reduced, along with a slightly lower peak HR (Table). The more striking decrease in the O_2 pulse during the last 4 minutes of exercise indicates a more rapid deterioration in the stroke volume response than in test 1. These findings suggest worsening of global ischemic burden (progression of obstructive CAD or decrease in microvascular reserve, or both).

At this point, more aggressive medical therapy was initiated with the addition of 20 mg of atorvastatin, 1 g of over-the-counter slow-release niacin, and 1 g of fish oil (omega-3 fatty acids) daily. Lipid analysis revealed marked improvement (LDL-C levels decreased by 57%, triglyceride levels decreased by 50%, and HDL-C levels increased by 22%). The patient remained entirely asymptomatic and continued this therapy for the next 3.3 years with no change in exercise or dietary habits from baseline.

TEST 3

The patient underwent CPET 3.3 years after test 2 to reassess cardiovascular status. In test 3, he performed the same 20-W ramp protocol and stopped exercising because of leg fatigue. He achieved a peak RER of 1.17, a peak HR of 86% of the predicted value, and a peak $\dot{V}O_2$ of 25.6 mL/kg/min (80% of predicted). His resting BP was 112/80 mm Hg, and BP at peak exercise was 190/92 mm Hg. No ST-segment changes or arrhythmias occurred during exercise. The response curves are represented in the Figure (test 3). In test 3, the contours of the response curves are markedly more normal (see normal reference in the Figure), suggesting improved LV function during exercise. $\dot{V}O_2$ increases linearly over the entire range of exercise, O_2 pulse continues to increase with WR and time, and HR increases linearly with $\dot{V}O_2$. In fact, the results of test 3 are normal. The improvement in LV function is further reflected by an increase in peak stroke volume (O_2 pulse at peak exercise) and peak cardiac output (peak $\dot{V}O_2$). Peak $\dot{V}O_2$ increased by 11% (percent of predicted $\dot{V}O_2$ increased by 21%), and O_2 pulse at peak exercise increased by 20%. Peak HR is almost identical between test 2 and test 3 (Table).

The dark downward arrows in the Figure demonstrate the onset of LV dysfunction and correspond to the hypothetical IT during exercise that is seen in tests 1 and 2, but not in test 3. The O_2 supply-demand ratio is normal to the left of

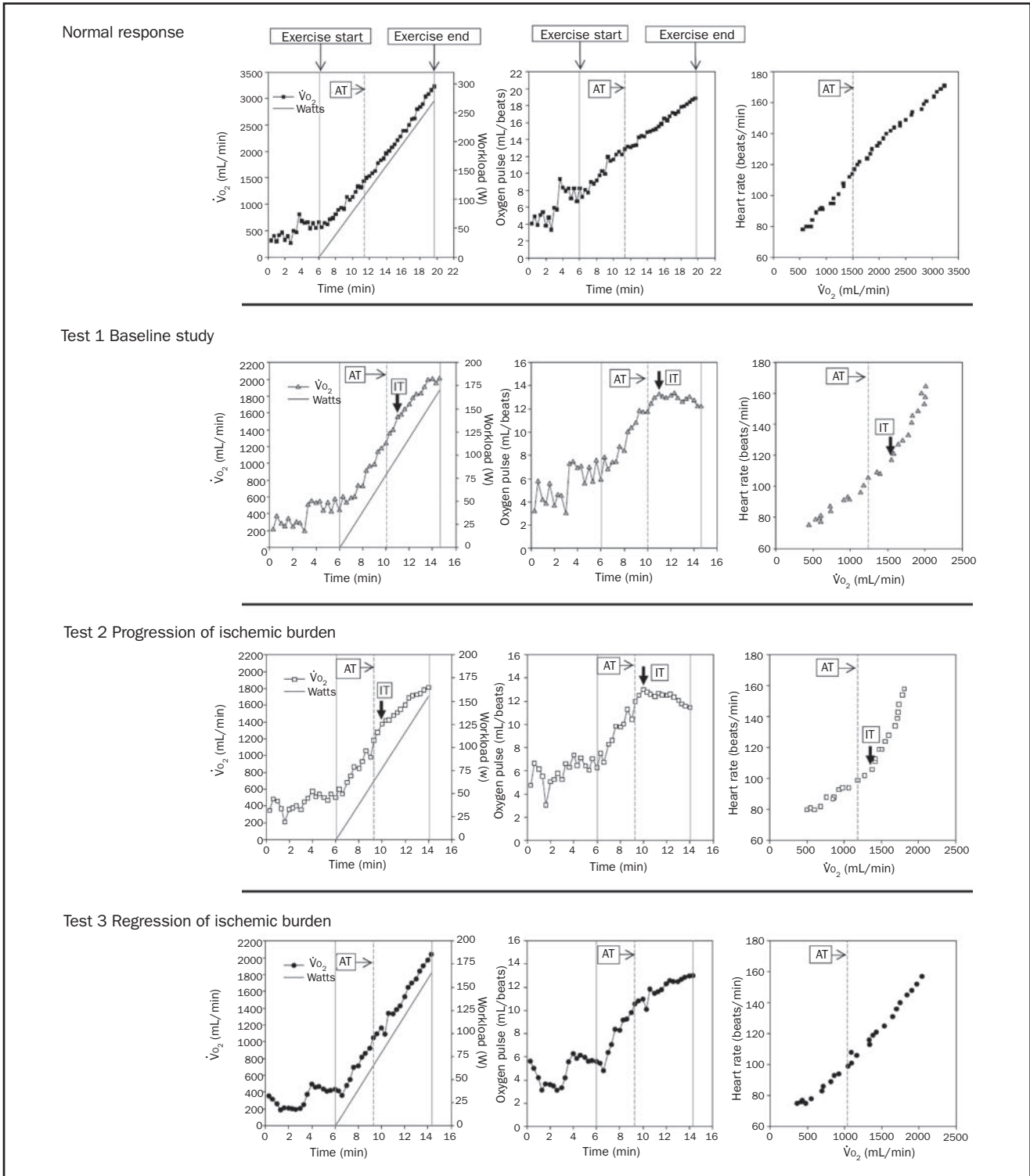


FIGURE. Changes in cardiopulmonary exercise testing (CPET) variables as related to time in a man with predisposition for coronary artery disease. Studies cover a 4.3-year period in which test 1 is baseline, test 2 is 1 year later, and test 3 is 3.3 years later. Test 1 shows early abnormality of exercise-induced myocardial ischemia, test 2 shows progression, and test 3 shows regression (ie, normalization) of the CPET variables. AT = anaerobic threshold; IT = ischemic threshold; $\dot{V}O_2$ = oxygen uptake. Oxygen pulse: $\dot{V}O_2/\text{Heart Rate} = \text{Stroke Volume} \times \text{Arteriovenous Oxygen Difference } [C(a-v)O_2]$. SI conversion factors: To convert $\dot{V}O_2$ and AT values to L/min, multiply by .001; to convert oxygen pulse to L/beat, multiply by .001.

TABLE. Serial Comparison of Cardiopulmonary Exercise Testing Parameters^a

	Work ramp (W/min)	Peak $\dot{V}O_2$ or peak cardiac output (% of predicted) ^b	WR at IT (W)	O ₂ pulse at peak exercise ^c (mL/beat)	Peak HR (beats/min)	Stress ECG response
Test 1	20	70	100	11.6	168	Normal
Test 2	20	66	75	11.0	156	Normal
Test 3	20	80	NA	13.2	155	Normal

^a ECG = electrocardiography; HR = heart rate; IT = ischemic threshold; NA = not available; $\dot{V}O_2$ = oxygen uptake; WR = work rate.

^b Predicted values were obtained from reference 4.

^c Oxygen pulse at peak exercise = peak $\dot{V}O_2$ /peak HR.

the down arrows, which is the reason that O₂ pulse (stroke volume) and $\dot{V}O_2$ (cardiac output) increase normally during early exercise. The LV becomes ischemic shortly after the AT, and the O₂ supply-demand ratio remains adequate up to the IT. At progressively higher workloads past the IT, the O₂ supply-demand deficit worsens, resulting in diastolic dysfunction followed by systolic dysfunction in the ischemic segments of the myocardium (the ischemic cascade). This phase would correspond to wall motion abnormalities observed on stress echocardiography. The net physiologic effect is a progressively worsening stroke volume response in each subsequent cardiac cycle with increasing WR due to intensification of myocardial ischemia.

DISCUSSION

Previous research in this area has focused on the utility of CPET to detect macrovascular ischemia due to epicardial CAD.⁵ To our knowledge, this case report is the first documentation of the use of CPET to clinically track progression of potential subclinical atherosclerosis in the primary prevention setting (test 1 to test 2) and then to assess the functional impact of pharmacologic interventions that decrease cardiovascular events and cause regression of coronary plaque in patients with CAD (test 2 to test 3).⁶⁻⁸

The findings of this case report have multiple implications, the first of which pertains to patient management. The use of CPET in this way represents a paradigm shift in current practice patterns: early detection of physiologic abnormalities during physical exertion and implementation of treatment without further evaluation. In light of recent outcomes trials comparing optimal medical therapy vs revascularization procedures,⁹⁻¹¹ further evaluation was not pursued because it would not have changed the fact that medical management was the most appropriate first-line therapy in this case, even if the patient was found to have multivessel CAD. The most compelling reason to intervene would have been to perform coronary artery bypass grafting if the patient had left-main or triple-vessel disease. Recent data suggest that even these patients do well with medical therapy.¹² The decision of when to proceed to coronary angiography would

have been determined primarily by a change in symptoms. We should also point out that findings on stress electrocardiography for our patient were unremarkable in all 3 tests, thereby providing no insight into his subclinical ischemia status and the ability to improve long-term management. Moreover, considering that estimation of functional capacity with traditional treadmill testing often overestimates actual functional capacity,¹³ aerobic capacity likely may have been considered to be within normal limits, and the changes measured in this case study would not have been appreciated without direct measurement of expired ventilatory gases. The primary value of CPET in this instance is the analysis of $\dot{V}O_2$ in relation to WR, O₂ pulse, and HR throughout the exercise test. Abnormal trajectory responses in these variables may serve as a valuable early indicator of LV dysfunction and a trigger for further evaluation or initiation of medical therapy in the primary prevention setting.

The second implication relates to prognosis. Currently, clinicians lack other effective noninvasive, cost-efficient, non-radiation-based examination techniques to gauge whether their long-term medical therapies are benefitting their patients on an individualized basis before the occurrence of the first cardiovascular event. Blood- and imaging-based measurements have not provided a clear, direct link between disease progression or regression, the threshold for inducible ischemia, and functional capacity, which are closely linked to prognosis. Although carotid intima-media thickness is used in the research setting as a surrogate marker for atherosclerosis to predict the risk of future events, this modality has raised clinical concerns. It is unknown whether a reduction in the progression, or a regression, of the carotid intima-media thickness after pharmacologic treatment is consistently associated with a reduction in cardiovascular events.¹⁴ Similarly, direct imaging of coronary anatomy with computed tomography or magnetic resonance angiography provides anatomic information but does not characterize the functional ramifications of inducible ischemia. In contrast, exercise capacity is well recognized in its ability to predict outcomes in both apparently healthy and chronic disease populations. Peak $\dot{V}O_2$ and peak O₂ pulse have been proven to be independent

predictors of mortality in patients with heart disease.¹⁵⁻¹⁷ These physiologic responses to exercise should predict the risk for future cardiovascular events more accurately than resting anatomic studies of the cardiovascular system. The detailed cardiovascular physiology data collected by CPET provide a mechanism to more precisely measure and quantify risk and relate to cardiovascular outcomes in a more direct manner. In the heart failure population, patients with a peak $\dot{V}O_2$ less than 50% of their age-predicted value have significantly higher short-term mortality rates than patients with a peak $\dot{V}O_2$ greater than 50%.¹⁸ Cardiopulmonary exercise testing detected LV dysfunction in a symptomatic woman in the complete absence of atherosclerosis on coronary angiography.¹⁹ In the same patient, serial CPET comparison demonstrated increased peak stroke volume and exercise capacity after treatment with anti-ischemic pharmacotherapy. Patients with nonobstructive CAD and decreased coronary flow reserve have been proven to be at increased risk of cardiovascular events.^{20,21} Treatment with disease-modifying anti-ischemic medical therapy and exercise below the IT (to prevent development of silent ischemia) can reverse endothelial dysfunction and improve microvascular reserve, which in turn can be documented with serial CPET comparison.

Development of ischemic heart disease is a chronic process that is a function of genetics, aging, and several lifestyle factors (diet, physical activity, and stress levels over time). During the 3.3-year treatment period, this patient did not change his lifestyle in any substantial manner. Therefore, the decrease in his ischemic burden was due primarily to medical treatment. Because of variability in the response of different individuals to different types of therapies, the magnitude of change observed in this case study may not be typical. Further investigation is needed to clarify the clinical value of this methodology for early disease detection, monitoring, and prognosis in a larger and more diverse patient population (asymptomatic and symptomatic individuals with macrovascular and/or microvascular ischemia). Nevertheless, early intervention is most likely to produce the best results for disease management and long-term cost containment. This methodology should also provide value in comparative effectiveness studies for the management of ischemic heart disease.

CONCLUSION

Evidence demonstrating the diagnostic value of CPET in patients with suspected or confirmed CAD continues to mount. This case study illustrates the potential value of CPET in the primary prevention setting to detect and track early-stage ischemic heart disease. Information obtained by CPET enables clinicians to improve the clinical management of

asymptomatic persons at risk of cardiovascular events on an individualized basis. Research in this area should continue to more firmly establish the clinical role of CPET in the evaluation of ischemic heart disease (macrovascular or microvascular) for the purpose of improving preventive cardiac care and thus reducing long-term health care costs.

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