A practical clinical approach to utilize cardiopulmonary exercise testing in the evaluation and management of coronary artery disease: a primer for cardiologists

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Word Count = 2607
Abstract

Purpose of Review:

There is growing clinical interest for the use of cardiopulmonary exercise testing (CPET) to evaluate patients with or suspected coronary artery disease (CAD). With mounting evidence, this concise review with relevant teaching cases helps to illustrate how to integrate CPET data into real world patient care.

Recent Findings:

CPET provides a novel and purely physiological basis to identify cardiac dysfunction in symptomatic patients with both obstructive (O-CAD) and non-obstructive (NO-CAD) coronary artery disease. In many cases, abnormal cardiac response on CPET may be the only objective evidence of potentially under-treated ischemic heart disease. When symptomatic patients have NO-CAD on coronary angiogram, they are still at increased risk for cardiovascular (CV) events. This problem appears to be more common in women than men and may warrant more aggressive risk factor modification. As the main intervention is lifestyle (diet, smoking cessation, exercise) and medical therapy (statins, ACE inhibitors, beta-blockers), serial CPET testing enables close surveillance of CV function and is responsive to clinical status.

Summary:

CPET can enhance outpatient evaluation and management of CAD. Diagnostically, it can help to identify physiologically significant obstructive and non-obstructive CAD in patients with normal routine cardiac testing. CPET may be of particular value in symptomatic women with NO-CAD. Prognostically, precise quantification of improvements in exercise capacity (EC) may help to improve long-term lifestyle and medication adherence for this chronic condition.

Key Words: Cardiopulmonary exercise testing ● Coronary artery disease ● Therapeutic monitoring
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<td>EECP</td>
<td>Enhanced external counter-pulsation</td>
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<td>PET</td>
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Introduction:

In the past decade, cardiopulmonary exercise testing (CPET) has seen an exponential increase in its evidence base for specific patient populations[1]. CPET for coronary artery disease (CAD) assessment is an area of growing clinical interest in which different parameters provide both diagnostic and prognostic insight for evaluation and management. The traditional diagnostic role of exercise stress testing has been to identify obstructive CAD (O-CAD) with the intent to revascularize culprit coronary lesions. Current strategies have focused on anatomical imaging with coronary computed tomography angiography (CCTA) with or without fractional flow reserve measurement (CCTA-FFR) and functional methods including stress ECG, stress echocardiography and myocardial perfusion imaging with ionizing radiation along with emergence of hybrid imaging of positron emission tomography (PET) together with computed tomography (Cardiac PET-CT). In outcomes analysis, direct coronary imaging with CCTA has shown reduced myocardial infarction (MI) compared with functional testing but without a reduction in mortality or hospitalizations at the expense of more frequent use of invasive procedures[2-4]. With the growing challenge of symptomatic non-obstructive CAD (NO-CAD) in clinical practice, these modalities have limited value. CPET helps to expand the role of exercise stress testing beyond identifying flow-limiting lesions. Diagnostically, it can help to confirm presence of cardiac dysfunction in symptomatic patients with 50% or less coronary stenosis which should act as a trigger for more aggressive risk factor modification to treat CAD. Prognostically, it enables close surveillance of cardiovascular (CV) status with serial testing whereby 10% increments in change in exercise capacity [i.e., peak oxygen consumption (VO₂)] can be quantified to measure response to lifestyle and medical therapy to ensure patients are responding to therapy and remain adherent long-term. Estimating exercise capacity (EC) lacks the precision needed to track longitudinal changes in patients acting as their own controls. This review addresses the clinical approach to utilize CPET in the evaluation and management of coronary artery disease.

Diagnostic Utility

The diagnostic utility of CPET to detect exercise-induced cardiac dysfunction lies in its’ ability for key variables to serve as surrogates for cardiac output (i.e., VO₂) and stroke volume (SV) (i.e., O₂-Pulse) as well as a direct measure of the heart rate (HR) response, in real-time per the Fick equation. Breath by breath analysis during a linear ramp protocol on a cycle ergometer enables detection of a normal vs. pathological response caused by CAD [5]. As described by the ischemic cascade, mechanical dysfunction precedes electrical changes and symptoms (Figure 1)[6]. Myocardial oxygen deficit during exertion causes mechanical dysfunction past the ischemic threshold resulting in SV to decrease with progressively increasing workload. To maintain peripheral perfusion to the exercising skeletal muscles, the autonomic nervous system upregulates sympathetic activity to accelerate HR as a compensation mechanism. This compensatory response in late exercise has been quantified as the change in HR to work rate slope parameter (ΔHR-WR Slope), comparing the HR slope in the last two minutes of exercise to
that in middle of exercise. This parameter as been demonstrated to be abnormal in symptomatic patients with non-obstructive (NO-CAD) as well obstructive (O-CAD) coronary artery disease[7]. Whereas healthy individuals have no change or deceleration of the HR response in late exercise (zero or negative ΔHR-WR Slope), symptomatic patients with varying degrees of coronary plaque have acceleration of their HR response (positive ΔHR-WR Slope; values >15% are pathological) in late exercise (Figure 2) [Met-test database]. In patients not capable of augmenting the HR response (advanced CAD, autonomic dysfunction and HR limiting medications causing chronotropic incompetence), the abrupt plateau or decrease in SV is accompanied by a decrease in cardiac output, reflected by VO₂, relative to work-rate (ΔVO₂/ΔWR slope flattens)[8, 9] and minute ventilation (i.e. the oxygen uptake efficiency slope – OUES)[10-12]. A more blunted VO₂ response is consistent with more severe disease.

The recognition of NO-CAD as an insidious condition that raises the risk for CV events has increased the urgency for a new approach to manage this growing dilemma, particularly in women[13-17]. Traditional functional stress testing (stress ECG, stress echocardiography and myocardial perfusion imaging) is not effective in detecting NO-CAD caused by diffuse microvascular ischemia[18-21]. Stress imaging studies were designed to detect relatively intense regional hypo-perfusion abnormalities but lose their sensitivity when the global ischemic burden becomes diffuse via multiple mechanisms including coronary endothelial dysfunction and decreased coronary flow reserve[22]. Sara et al reported that approximately two-thirds of men and women with NO-CAD and normal routine stress studies had microvascular dysfunction proven with functional coronary angiograms over a 20-year period [23]. Cardiac PET can identify decreased coronary flow reserve (CFR) in patients without significant obstruction and decreased CFR predicts increased CV risk[24, 25]. Whether or not the abnormal SV and HR patterns observed in symptomatic patients with NO-CAD on CPET is due to microvascular ischemia is an area in need of further evaluation and correlation with CFR and coronary endothelial dysfunction is necessary.

The main clinical advantage that CPET offers over other cardiac tests to diagnose ischemic heart disease (IHD) is its’ ability to prove that NO-CAD is causing physiologically significant inducible myocardial dysfunction, implying that symptoms are cardiac and likely due to under-treated CAD in symptomatic patients with normal routine testing. Relying on the body’s natural compensation mechanism to identify under-treated atherosclerotic heart disease is a novel concept and has potential to improve preventive care as this information can be used to implement more aggressive exercise and medical treatment for CAD, particularly when symptoms are vague (anginal equivalents). Figure 3 demonstrates cardiac dysfunction on CPET in a patient with myocardial infarction with NO-CAD (MINOCA)[Met-test database]. She had a three-year history of shortness of breath with normal routine outpatient cardiac testing. Her symptoms were not recognized as an anginal equivalent and the window to intensify atherosclerosis modifying therapy was missed resulting in preventable morbidity to the patient and increased costs to the healthcare system. Interest in augmenting outpatient exercise intolerance evaluation with CPET is growing. The Mayo Clinic now offers CPET in conjunction with nuclear myocardial perfusion imaging (MPI + CPET) as a single test. The main motivation was not to enhance the evaluation of ischemic heart disease but to identify non-ischemic
etiolologies of symptoms (deconditioning, pulmonary, diastolic dysfunction). They reported that almost three-fourths of normal nuclear MPI studies had abnormal CPET findings that helped improve clinical care[26].

Prognostic Utility for Therapeutic Monitoring

The main aim of any intervention is to improve prognosis, limit morbidity, and maintain a higher quality of life, all of which are markers associated with high peak VO$_2$ values. In fact, due to a robust evidence base, peak VO$_2$, also defined as cardiorespiratory fitness (CRF), has been proposed as a vital sign[27]. There is a strong, inverse, and independent association between peak VO$_2$, or CRF, and the first nonfatal MI and subsequent heart failure risk, with significant risk reclassification by this primary CPET variable [28]. CRF as determined by direct measurement of peak VO$_2$, exerts a major long-term influence on prognosis in men after MI, CABG, or IHD and can play a valuable role in risk stratification and counseling[29]. In women with CAD, considered as a continuous variable, a 1 mlO$_2$•kg$^{-1}$•min$^{-1}$ advantage in initial peak VO$_2$ was associated with 10% lower cardiac mortality[30]. In absolute terms, patients with a peak VO$_2 < 16$ mlO$_2$•kg$^{-1}$•min$^{-1}$ at time of discharge after MI and post-PCI have been shown to be at increased risk for adverse events over two years[31]. With excellent reproducibility of peak VO$_2$ measurements in the CAD population[32], the goal in each individual should be to increase this vital sign from baseline for longevity[27]. Peak VO$_2$ is a variable that is responsive to therapy, and serial measures are potentially valuable in close surveillance of CV health status. Individuals whose peak VO$_2$ increases between examinations have a lower risk of adverse health and clinical outcomes than those whose peak VO$_2$ decreases, and this should be communicated to patients[27].

Exercise as a therapeutic modality

Exercise has a multitude of physiological benefits in cardiac patients (Table 1). It improves cardiac function (i.e., SV and HR response) as well as skeletal muscle perfusion and oxygen utilization (peripheral extraction = C(a-v)O$_2$). A large meta-analysis recently confirmed that exercise-based cardiac rehabilitation reduces cardiovascular mortality, hospital admissions (along with associated health care costs) and improves quality of life[33]. However, cardiac rehabilitation remains under-utilized and more favorable outcomes are equated to larger increases in peak VO$_2$ [34, 35]. In general, the greater the activity amount or intensity, the greater the increase in peak VO$_2$. CAD-patients who perform regular moderate physical exercise ≥150 min/week have significantly better left ventricular diastolic function and higher peak VO$_2$ peak than patients with <150 min/week exercise and higher weekly physical exercise outweighs the other modifiable CV risk factors of obesity, diabetes and hypertension[36]. Exercise training may constitute a relevant therapeutic strategy in patients with microvascular angina. A recent pilot study demonstrated that exercise training that increased mean peak VO$_2$ by 12% was associated with significant reduction of reversible ischemic myocardial perfusion defects on SPECT in patients with angiographically normal coronaries along with improvement
in quality of life[37]. *Figure 4* highlights key exercise physiology parameters to monitor with serial testing and demonstrates a dramatic response to cardiac rehabilitation in a highly motivated 57-year-old male after 3-vessel coronary bypass graft surgery [Met-test database].

**Precise Exercise Prescriptions:** Defining the moderate intensity exercise HR zones for CAD patients as the starting point of an exercise rehabilitation program is crucial. This can be a daunting task considering that more severe CAD patients have intrinsic chronotropic incompetence and many are on HR-limiting agents. CPET offers the unique ability to define individualized specific HR zones that correspond to moderate intensity exertion (40-60% of VO$_2$ reserve) thereby targeting work zones that are safe and therapeutically effective.

**Monitoring Medical Therapy**

A recent observational study in 9136 patients (61% women) with MINOCA reported long-term outcomes results on medical therapy for secondary prevention. Findings revealed significant benefit from statin (23% reduction) and ACE inhibitor (ACE-I)/ARB therapy (18% reduction) and borderline benefit from beta-blocker therapy (14% reduction)[38]. Current ACC/AHA guidelines recognize the therapeutic benefits of various pharmacological interventions to improve functional capacity. Exercise time has proven to be a discriminating test for many antianginal therapies and is recommended for this purpose by both the US Food and Drug Administration and the European Medicines Agency. Statins, ACE inhibitors and beta-blockers have reduced morbidity and mortality in patients with atherosclerotic heart disease and are the cornerstones of preventive medical therapy for this population. In theory, any therapy that improves coronary microcirculation should result in improved myocardial perfusion, contractility, higher peak SV and therefore higher peak VO$_2$ over time. Ranolazine has been shown to improve CFR and peak VO$_2$ in patients with microvascular angina[39, 40]. Coronary microvascular function quantified by CFR has been independently associated with peak VO$_2$ in obese CAD patients[41]. Enhanced external counter-pulsation (EECP) therapy decreases angina episodes and improves quality of life in patients with systolic dysfunction and one study elucidating the mechanism of these findings demonstrated improved endothelial function and dramatic increase in peak VO$_2$ (+36%) after 35 sessions[42]. ACE inhibitors improve CFR in symptomatic women with NO-CAD over 4 months[43] and ACE-I along with ARBs significantly improve peak VO$_2$ on their own and have led to greater enhancements when taken together[44]. Rosiglitazone improves endothelial function and peak VO$_2$ in diabetics after 4 months of therapy [45]. While beta-blockers blunt the HR response to physical exertion, previous research has found a significant increase in peak VO$_2$ still occurs in post MI and heart failure patients who participate in an exercise training program[46]. Metformin improves ventilatory efficiency in non-diabetic heart failure patients with insulin resistance[47]. Of note, therapies that improve resting parameters but not exercise capacity are of questionable clinical value. In the ALDO-DHF trial, long-term aldosterone receptor blockade improved resting left ventricular diastolic function but did not affect maximal exercise capacity and hence patient symptoms, or quality of life in patients with heart failure with preserved ejection fraction[48].
Given the associated improvements in key prognostic CPET variables with the initiation of pharmacological therapy, it may be interesting to explore the feasibility of titrating medications based on CPET “responders” or “non-responders” in future clinical trials. The frequency at which a patient should perform CPET evaluation to monitor the effectiveness of interventions is not well-defined. In clinically stable patients, CPET might be considered at 2- to 4-year intervals, whereas in patients with signs and symptoms, the test might occur in a time frame that has been reported to cause significant improvements in the variable of interest[49].

**Figure 5** illustrates changes in key CPET parameters with serial testing for longitudinal tracking in an at-risk asymptomatic individual found to have significant cardiac dysfunction and low peak VO₂ on baseline CPET. After 3.3 years of medical therapy on statin and niacin, there was significant improvement in cardiac dysfunction and peak VO₂; addition of exercise rehab almost completely normalized these parameters by year 7 [Met-test database]. **Figure 6** demonstrates the distribution of change in peak VO₂ in 225 firefighters tested one year apart. The 20 patients with >20% decrease in peak VO₂ are of particular concern and should be singled out for further evaluation and treatment [Met-test database]. Exercise therapy alone has potential to change the trajectory of these individuals with rapidly worsening prognosis.

**Obstructive CAD and Revascularization**

Cardiac dysfunction detected by CPET is a function of global ischemic burden given that the abnormalities in SV and HR are seen in symptomatic patients with both NO-CAD and O-CAD[7]. Men had the highest rate of revascularization in this study and their mean peak VO₂ was 68% of predicted. ‘Balanced Ischemia’ seen in patients with diffuse O-CAD (triple vessel and left main disease) is a challenging condition for imaging based stress testing to detect due to the non-regionalized nature of the ischemic burden. These patients are some of the highest risk patients and tend to have decreased peak VO₂. Coronary angiogram should be considered in symptomatic patients with normal stress imaging and cardiac dysfunction with reduced peak VO₂ (<70% of predicted) on CPET. Coronary CTA with FFR [50]may be the ideal next study in such individuals as patients in need of revascularization can be singled out and patients with NO-CAD can undergo exercise and medical therapy with close surveillance to ensure that peak VO₂ and prognosis is improving over time. Continuous regular feedback with set goals for future peak VO₂ values has the potential to improve patient adherence with lifestyle changes and medications. The effect of revascularization on peak VO₂ would be an area of interest with the current paucity of information. The results of ORBITA, the only blinded, randomized placebo-controlled trial of PCI, show that in patients with angina and single vessel coronary stenosis, exercise capacity (measured by CPET) and symptoms were not improved significantly compared with placebo intervention[51]. In patients with multi-vessel CAD, one study comparing complete vs. incomplete revascularization with PCI in patients after MI did not show significant short-term differences on CPET between the two approaches[52]. These data lend credence to the hypothesis that increasing peak VO₂ is more likely a function of other mechanisms (including the micro-circulation) rather than macro-circulation and that
therapeutic interventions should move beyond the stenosis-centric frame to optimize outcomes.

Conclusion

In conclusion, there is a robust body of evidence demonstrating the clinical value of CPET in a number of patient populations, including those with cardiovascular disease. Key CPET variables hold powerful diagnostic and prognostic utility in patients with cardiovascular disease. CPET also holds considerable promise in gauging the response to a broad range of therapies, including pharmacologic, surgical and lifestyle interventions. Improving the CPET response, in particular peak VO₂, may evolve into a primary treatment goal in patients with cardiovascular disease if future randomized trials support this approach.

Key Points:

- Cardiopulmonary exercise testing (CPET) is a clinically valuable assessment in patients with suspected or confirmed coronary artery disease
- CPET may hold particular utility in identifying and tracking health status in patients with non-obstructive coronary artery disease – a fertile area for future research
- CPET may have strong diagnostic and prognostic value as well as the ability to gauge therapeutic efficacy, topics that warrant further randomized assessment

Acknowledgments

None

Financial Support and Sponsorship

There was no funding associated with this article.

Conflicts of Interest

Sundeep Chaudhry is an employee and owns equity at Met-test.

Naresh Kumar is an employee and owns equity at Whitby Cardiovascular Institute.

Dr. Deepak L. Bhatt discloses the following relationships - Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Cleveland Clinic, Duke
Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine, Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today’s Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Ironwood, Ischemix, Lilly, Medtronic, Pfizer, Roche, Sanofi Aventis, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald’s Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott); Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, PLx Pharma, Takeda.

The remaining authors have no conflict of interest.

References


*First paper to describe abnormal acceleration of heart rate response during late exercise in symptomatic patients with suspected CAD compared to a normal cohort. This abnormal compensatory response is physiologically indistinguishable between patients with obstructive and non-obstructive CAD and is consistent with under-treated atherosclerotic heart disease.


*Outcomes data showing that patients with NSTEMI and non-obstructive CAD have a comparable prognosis to patients with one- or two-vessel disease and patients with diffuse atherosclerosis have worse prognosis than those with angiographically normal coronary arteries.


*Patients with NO-CAD are potentially under-treated and require more specific management.


*Symptomatic patients with NO-CAD often have persistent chest pain and impaired quality of life requiring novel strategies to improve health outcomes.


*MI without obstructive coronary disease is common (~1 in 9 patients) and has an adverse outcome rate 12 times that of age and sex matched patients without CAD.
**Excellent review paper highlighting extensive data in the literature that cardiorespiratory fitness (CFR) is a powerful clinical vital sign for all-cause mortality and accurately reclassifies risk for adverse outcomes independent of traditional CV risk factors. The underlying premise is that the addition of CFR for risk classification presents health professionals with unique opportunities to improve patient management and to encourage lifestyle-based strategies.


*This study confirms that exercise-based cardiac rehabilitation reduces cardiovascular mortality and provides important data showing reductions in hospital admissions and improvements in quality of life that are consistent across patient and intervention types.


* CAD-patients who perform regular physical exercise ≥150 min/week have significantly better resting left ventricular diastolic function and peak VO2 independent of many traditional CV risk factors.


*Physical training is associated with reduction of reversible ischemic myocardial perfusion defects in patients with microvascular angina. This positive effect was accompanied by significant improvement of the functional capacity and quality of life. The results of this pilot study indicate that physical training may constitute a relevant therapeutic strategy in this population.

** This long-term observational study in MINOCA patients indicates beneficial effects of treatment with statins and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers on outcome in patients with MINOCA, a trend toward a positive effect of β-blocker treatment, and a neutral effect of dual antiplatelet therapy. Medical management is the mainstay for improving outcomes in patients with symptomatic non-obstructive CAD just as it is in obstructive CAD.


*This review highlights modern CPET use as a single or combined test that allows the pathophysiological bases of exercise limitation to be translated into clinical practice.


**First trial comparing PCI with placebo (sham procedure) to relieve angina and increase exercise capacity in individuals with angina and severe single vessel disease with CPET as the primary endpoint.** Surprisingly, the results revealed that CPI did not improve symptoms or increase exercise time or peak VO2 compared to placebo and called into question the clinical value of PCI in patients with single vessel disease. The results cannot be generalized to multi-vessel disease.


**Figure Legends**

**Figure 1**

This figure demonstrates the sequence of metabolic derangements that occur when the myocardium becomes oxygen deprived with progressively increasing workload.

ATP = adenosine triphosphate; Ca^{2+} = Calcium; ECG = electrocardiogram

**Figure 2**

A. Heart rate (HR) and stroke volume (SV) assessments in a healthy 45-year-old male with no heart disease and no cardiovascular risk factors. Note the high peak linear SV response (blue line) with deceleration of HR slope (negative ΔHR-WR Slope – red line) after the anaerobic threshold (AT).

B. Heart rate (HR) and stroke volume (SV) assessments in a 58-year-old female patient after myocardial infarction, multiple stent placements and prior to entry into cardiac rehab program. This study was performed on beta-blocker therapy. She achieves a normal peak SV but has a decreasing trend with acceleration of HR slope (positive ΔHR-WR Slope) after the AT demonstrating persistent cardiac dysfunction after revascularization.

HR = heart rate; O2-pulse = oxygen pulse (VO2/HR); ΔHR-WR Slope = change in HR slope in last 2 minutes of exercise compared to HR slope at AT; AT = anaerobic threshold; bpm = beats per minute.

**Figure 3**

Cardiac dysfunction in a 53-year-old African-American female who presented to the ER with non-ST elevation myocardial infarction. CPET abnormalities include plateau of O2-pulse with low
peak value with corresponding acceleration of HR-WR slope in late exercise. Coronary angiogram revealed only minor irregularities. This study was performed on beta-blocker therapy upon entry into cardiac rehab. The dysfunction pattern would be more pronounced off of beta-blockers.

HR = heart rate; O2-pulse = oxygen pulse (VO2/HR); ΔHR-WR Slope = change in HR slope in last 2 minutes of exercise compared to HR slope at AT; AT = anaerobic threshold; bpm = beats per minute.

Figure 4

Pre-and post-cardiac rehab snapshot of a 57-year-old male who underwent 3-vessel bypass surgery. This individual had hypertension, hyperlipidemia and was sedentary prior to surgery. He was highly motivated during rehab and was jogging by end of 3-month rehab. Changes: Resting HR decreased from 100 to 80 bpm; acceleration in HR-WR slope completely normalized in test 2; peak VO2 increased 57%; peak O2-pulse increased 42% to predicted normal value; peak HR increased 11% and anaerobic threshold (AT), an effort independent measure of aerobic capacity increased by 42%.

HR = heart rate; O2-pulse = oxygen pulse (VO2/HR); ΔHR-WR Slope = change in HR slope in last 2 minutes of exercise compared to HR slope at AT; AT = anaerobic threshold; bpm = beats per minute.

Figure 5

Serial comparison data of an individual acting as his own control; CV risk factors included a strong family history (almost all male relatives with CAD shortly after age 40), hyperlipidemia and sedentary lifestyle.

Test 1: Baseline study at age 36 without symptoms demonstrating pronounced cardiac dysfunction with low peak VO2. Note the pronounced drop in SV response just after the AT resulting significantly reduced peak O2-pulse. HR-WR response accelerates concurrently with 98% increase in slope from baseline.

Test 2. Repeat study after 3.3 years of medical therapy with statin + niacin with no change in lifestyle. Lipids improved dramatically and repeat CPET demonstrates less cardiac dysfunction with improved SV response resulting in 12% higher peak VO2 (ml/kg/min) and peak O2-pulse (ml/min) with less acceleration of HR-WR slope (compensatory response has diminished).

Test 3. Motivated by improvement in test 2, this person started regular exercise with cross-fit regimen. Test 3 is 4.5 years after test 2 and represents effect of exercise in addition to continuing lipid therapy. Absolute peak VO2 increased 30%, peak O2-pulse increased 15% and there is borderline LV dysfunction with marginal acceleration of HR response after the AT. This
individual has better CV function at age 42 than he did at 36 and may have improved his long-term prognosis, quality of life and healthcare costs.

HR = heart rate; O2-pulse = oxygen pulse (VO2/HR); SV = stroke volume; ∆HR-WR Slope = change in HR slope in last 2 minutes of exercise compared to HR slope at AT; AT = anaerobic threshold; bpm = beats per minute.

Figure 6

Change in peak VO2 in 225 firefighters tested one year apart. The 20 individuals that had > 20% decrease should be of particular concern and should warrant more aggressive risk assessment with intervention.

∆ peak VO2 = change in peak VO2 between two serial tests approximately one year apart.