**Exercise Testing and Coronary Disease: Pushing Fitness to Higher Peaks**

Sanjay Sharma BSc (Hons), MBChB, MD, FESC

Aneil Malhotra MB BChir, MA (Hons), MSc, PhD

Cardiology Clinical and Academic Group, St George’s, University of London, Cranmer Terrace, London SW17 0RE, UK

Address for correspondence

Sanjay Sharma MD, FESC

Cardiology Clinical and Academic Group, St George’s, University of London, Cranmer Terrace, London SW17 0RE, UK

Tel: 020 8725 1390.

E-mail address: sasharma@sgul.ac.uk

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Participation in regular physical activity is associated with a lower incidence of cardiovascular deaths compared with the sedentary population. Such benefits also apply to individuals with established risk factors for atherosclerotic cardiovascular (CV) disease1 including those with markedly increased coronary artery calcium scores.2 Although cardiorespiratory fitness (CRF) has a genetic component, it is a surrogate marker of habitual physical activity. Improving CRF through increased physical activity accrued from general day-to-day activities, or from a concerted effort to exercise regularly, attenuates acquired risk factors for atherosclerosis such as obesity, metabolic syndrome, hypertension and hyperlipidaemia. Additionally, regular exercise produces several beneficial effects on autonomic profile, systemic vasculature, skeletal muscle, inflammatory markers and hormonal profile to mention a few, therefore, it is not a surprising independent predictor of CV mortality, all-cause mortality and possibly, longevity of life.3

Traditional measures of CRF have relied on estimation of metabolic equivalents (METs) from subjective reports of physical activity or from conventional treadmill or bicycle tests.1,4 Few studies have used simultaneous cardiopulmonary gas exchange measurements to determine, peak oxygen consumption (pVO2), which is considered the “gold standard” for assessing CRF. Existing studies utilising pVO2 were conducted in relatively small cohorts, or estimated pVO2 from anthropometric data.3

In this edition, Letnes and colleagues5 report the association between pVO2 and fatal and non-fatal coronary heart disease (CHD) in a subset population of 4,527 healthy Norwegian adults who were enrolled in the larger Nord-Trondelag Health Study (HUNT3).6 Participants were aged 48.2 ± 13.5 years and 51% were female. All participants were reportedly free from cardiovascular or respiratory disease, cancer and hypertension. The vast majority (83.5%) had a low ten-year risk of cardiovascular disease at baseline. The mean VO2 peak values were 44.4 and 36.0ml/kg/min (12.7 and 10.3 METS respectively) for men and women respectively and 80% achieved the maximal predicted oxygen consumption for age and size indicating that this was considerably fitter cohort compared with a previous studies1 that have investigated the relationship between CRF and CHD. Over a follow up period of 8.8 years, 147 (3.2%) subjects reached the primary end-point of a diagnosis of CHD, coronary revascularization, or death from CHD. There was an overall 15% lower risk of meeting the primary end-point per one-MET higher pVO­2 after adjusting for sex and 16% lower risk per one MET when additionally adjusted for established risk factors. This figure is very similar to other studies investigating older individuals with a higher burden of CV risk factors and lower CRF.1 In this study, women showed a slightly attenuated effect presumably because they were similar in age yet develop clinical CHD around 10 years later than men. Furthermore, a larger proportion of women had a low 10-year risk profile (94.3% vs 72.3%) and fewer achieved primary end points (105 vs 42) compared with men respectively. Between the highest and lowest quartile of pVO2, there was a 48% lower risk of a fatal or non-fatal CHD event. Other cardiopulmonary gas exchange parameters such as oxygen pulse and ventilatory equivalents of oxygen and carbon dioxide also demonstrated significance in predicting the primary end-point. The authors conclude that even among a healthy, low-risk population, pVO2 was inversely associated with CHD.

The investigators studied a relatively large subset of fit healthy individuals and CRF was determined with pVO2 which is recognised as the most accurate objective marker of fitness. During a follow up of 40,000 person-years, data pertaining to primary end points were obtained from mandatory national registries which strengthens the validity of the results. Furthermore, 51% of the cohort were women, in whom there is a paucity of population-based data. Whereas previous studies have focused on individuals achieving ≤ 12 METS, we estimated (supplementary table 2) that approximately 60% men and 50% women in this study achieved > 12 METS and > 10 METS respectively. Indeed, within the highest quartile, men achieved 17-21.5 METS and women achieved 13.8-19 METS.

Previous studies in participants with recognised risk atherosclerotic risk factors have revealed a 12-20% reduction in CV events per one MET achieved with an ongoing inverse relationship up to 12 METS. This study adds to current literature by demonstrating a similar benefit in an ostensibly healthy population with an incremental benefit that continues beyond 12 METS and suggests that there is no obvious upper threshold for the cardioprotective effects of exercise.7

Although the number of subjects is laudable there are several points to note. Only a third of eligible low risk participants volunteered for and completed the cardiopulmonary exercise stress test hence there is an unavoidable but inherent selection bias towards those who were motivated to attend for functional cardiac assessment and who were arguably more aware of lifestyle measures to mitigate cardiovascular disease.

The cohort consisted of a relatively young healthy population with a low 10-year CV event risk therefore a follow-up period of 8.8 years is modest. These factors may partly explain the low incidence of the primary end-point. Despite the authors postulating that their findings support several biological mechanisms through which CRF affects multiple organ systems, this study did not demonstrate any difference between pVO2 and all-cause mortality. Apart from the young age of the population, we believe that a highly selected low risk population without overt features of cardiac and respiratory disease is the most likely explanation this lack of association. Based on the pVO2 values provided (supplementary table 2), a considerable proportion of participants in their seventh and eight decades would have achieved much higher than predicted values for age, demonstrating an overall healthy cohort with a lower than expected all-cause mortality during the follow up period.

A very recent study enrolled over 5000 Danish males of a similar age to this cohort and followed them up for 46 years.3 During this period 4,700 (92%) men died (42% from CV disease). Men with high-normal or above normal estimated pVO2 values lived 2.9 years and 4.9 years longer respectively compared to men with below normal pVO2 values and this effect was consistent for CV deaths and all-cause mortality. These results suggest that early benefits of CRF noted by Letnes and colleagues and likely to persist into sixth, seventh, eighth and ninth decades if CRF is maintained.

Letnes and colleagues largely reinforce what is known already. Cardiorespiratory fitness is inversely related to coronary heart disease, even among a healthy population. This holds true whether physical activity is determined through systematic health questionnaires, conventional exercise tests or utility of pVO2 and is applicable to both sexes and individuals with established risk factors and subclinical CV disease. The additional benefit of adding peak VO2 to standard risk stratification scores in this population was slight but we suspect that a larger study with longer follow up would have provided stronger predictive value. Nevertheless, in an era where primary prevention is playing an increasingly significant role in society, this study helps highlight that improving CRF is a pivotal factor in reducing CV risk and mortality. Regular physical activity and measures of CRF should be incorporated into clinical practice and CV risk models. All individuals should be encouraged to exercise to the minimal level recommended by the European guidelines for disease prevention8 although the observations of Letnes and colleagues and several others suggest that substantially higher physical activity levels and CRF are provide additional prognostic benefit.9 For those who are compromised due to comorbidities or functional status, there is overwhelming evidence that some physical activity is better than none.

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**Figure legend- The impact of cardiorespiratory fitness in healthy middle-aged men and women.**

CHD= coronary heart disease; MET= metabolic equivalent.