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Editorial

# Detection of exercise induced ischaemia: a new role for cardiopulmonary exercise testing

J.-P. Schmid\*

Swiss Cardiovascular Center Bern, Cardiovascular Prevention & Rehabilitation, University Hospital (Inselspital), 3010 Bern, Switzerland

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The exercise stress test has been used for decades as a diagnostic tool in the work-up of patients with suspected coronary artery disease. Even though the traditional exercise electrocardiogram is a widely accepted and well-validated diagnostic tool, it suffers from low sensitivity, which nevertheless depends strongly on the population tested. When a work-up bias is avoided (that means, the test is applied to individuals not already known to have coronary artery disease), the sensitivity can be as low as 45% with a specificity of 85%.<sup>1</sup> In patients with an angiographically significant coronary artery disease and a horizontal or downsloping ST-depression of 1 mV (1 mm), in a meta-analysis a mean sensitivity of 66% has been described with a range between 40% and 90% for 1-vessel to 3-vessel disease and a corresponding mean specificity of 84%.<sup>2</sup>

Because of the low sensitivity of the exercise stress test, a lot of specialists risk to be misled to apply more expensive, time-consuming and potentially risky diagnostic procedures. In this issue of the European Heart Journal, to overcome the disadvantages of the standard exercise stress test, Belardinelli et al.<sup>3</sup> report about the application of a new element to detect exercise-induced ischaemia, namely the analysis of respiratory gas during the exercise stress test. In their effort to ameliorate the diagnostic accuracy of exercise stress testing, they take advantage of the concept

of the ischaemic cascade, which has already been recognized for several decades and describes the impact of the pathophysiologic manifestations of ischaemia on left ventricular function. After reduction in myocardial blood flow sufficient to result in ischaemia, a predictable sequence of events occurs. The first mechanical consequence of the metabolic changes at the onset of ischaemia is diastolic dysfunction, followed by wall motion abnormalities and a subsequent rise in left ventricular filling pressure. This occurs well before ECG changes are registered or chest pain is reported.

The increase of  $VO_2$  with incremental work load is linear in the normal subject and a function of heart rate, stroke volume and the difference of arterio-venous oxygen concentration. According to Fick's law ( $VO_2 = \text{cardiac output} \times \text{arterio-venous } O_2 \text{ difference}$ ), the non-invasive measurement of oxygen uptake allows conclusions about cardiac output. Therefore, a decline of the ejection fraction and consequently the cardiac output during exercise, will lower the rate of increase of  $VO_2$  and cardiopulmonary exercise testing (CPET) should allow the detection of ischaemia, even in case of a non-conclusive ECG and/or silent ischaemia.

In their study, Belardinelli et al. report about 202 consecutive patients with documented coronary artery disease, in whom an incremental exercise stress test with breath-by-breath gas exchange analysis, followed by a 2 day stress/rest gated SPECT myocardial scintigraphy was effectuated. Two variables were found to improve the sensitivity of the stress test: the decline in the rate of increase of  $VO_2$  proportional to work load change

\* Corresponding author. Tel.: +41-316-328-972; fax: +41-316-328-977  
E-mail address: jean-paul.schmid@insel.ch (J.-P. Schmid).

( $\Delta\text{VO}_2/\Delta\text{work}$ ) and  $\text{O}_2$  pulse flattening duration, calculated from the onset of myocardial ischaemia to peak exercise. That way the sensitivity of standard ECG stress testing in identifying exercise-induced myocardial ischaemia increased from 46% to 87%, and the specificity from 66% to 74% (64% for women respectively).

Thus, the authors were able to combine the well known physiologic law of linear increase in oxygen consumption during exercise with the pathophysiologic steps of the ischaemic cascade and to correlate it successfully with an imaging technique. This translation of profound understanding of pathophysiologic mechanisms and the technical possibilities of CPET into a new investigational concept could serve as a landmark study in the exercise-testing domain concerning the detection of ischaemia. Hopefully, this study will promote the application of CPET as a non-invasive tool in the work up of patients with suspected coronary artery disease and thus valorise this test.

During the last years, cardiopulmonary stress testing has already gained more and more interest among cardiologists. By means of  $\text{O}_2$  uptake and  $\text{CO}_2$  production together with minute ventilation measurement, it allows an integrative assessment of cardiovascular performance, pulmonary function and peripheral muscular condition, which has led to an extension of the diagnostic possibilities. Actually, CPET in cardiology is applied mainly in patients with heart failure where it has been shown to be of great value in the appreciation of prognostically important parameters (for example  $\text{VE}/\text{VCO}_2$  slope and peak  $\text{VO}_2$ ) or in the setting of cardiac rehabilitation, where the assessment of maximal physical work capacity, determination of the anaerobic threshold and evaluation of exertional dyspnoea are in the foreground.

The great prognostic information offered by the exercise stress test compared with other techniques in the evaluation of stress induced myocardial ischaemia is a big advantage. Exercise capacity has been shown to be one of the most potent predictors of mortality<sup>4</sup> and also heart rate recovery has consistently shown its prognostic usefulness.<sup>5</sup> Furthermore, chronotropic incompetence, that is an attenuated rise in heart rate during exercise, is at least as prognostically ominous as a nuclear perfusion abnormality,<sup>6</sup> while ST-segment changes alone have not emerged as an independent risk predictor.<sup>7</sup>

The prognostic and diagnostic value of the exercise test is maximized, when multiple exercise findings are considered and it seems, that respiratory gas analysis offers new perspectives in this sense.

Cardiologists should realise that with CPET we have an enormously powerful tool to our disposal. When we evaluate a patient without a revascularization history, one of the most important tasks is to assess his risk.<sup>8</sup> It makes no sense to institute invasive therapeutic procedures in patients who are already at low risk. On the other hand in front of a patient with known coronary artery disease who has undergone an angioplasty with stent implantation and complains about rather atypical chest pain several months later, the course of the  $\Delta\text{VO}_2/\Delta\text{work}$  slope and/or the presence of an  $\text{O}_2$  pulse flattening during the exercise stress test will be of great help when to decide, whether conservative management and reassurance is appropriate or if a restenoses has to be excluded by angiography.

As Belardinelli and coworkers state in the introduction of their article, until now there has been some reluctance to use CPET, mainly because of lacking routine in interpretation of the results, the time requirements of the test and technical aspects. This will remain a barrier to introduce CPET into clinical routine, but further simplification of the system's handling and growing popularity of CPET will certainly change this circumstance and pave the way to success, assumed that the new indication will assert itself.

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