

ResETTING the diagnostic utility of exercise tolerance testing for INOCA

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Exercise tolerance testing (ETT) is an important diagnostic and prognostic tool for assessing patients with suspected coronary artery disease (CAD). During exercise, coronary blood flow increases to meet the heightened metabolic demands of the myocardium. Limiting the coronary blood flow, and thus myocardial perfusion, results in electrocardiographic changes reflective of tissue ischaemia. Classically, the major limitation of ETT has been the poor specificity of ST-segment changes as an indicator of myocardial ischaemia. ST-segment depression has been estimated to occur in up to 20% of tested individuals on electrocardiographic monitoring. There are numerous causes of ST-segment changes, apart from CAD, which confound the result of exercise testing. Baseline resting electrocardiogram (EKG) abnormalities, as well as repolarisation and conduction abnormalities, may preclude an accurate interpretation of the ETT EKG. As a result, amongst patients with an intermediate pretest risk of CAD, ETT has the lowest sensitivity and specificity to detect obstructive CAD compared to thallium, single-photon emission computed tomography (SPECT) perfusion, stress echocardiography, and positron emission tomography (PET) imaging¹. Herein lies the problem.

The diagnostic accuracy of ETT has been judged on the correlation of specific EKG changes with the finding of obstructive CAD on coronary angiography. We understand that this is a suboptimal standard, as obstructive atherosclerosis is not the exclusive cause of myocardial ischaemia. Ischaemia with non-obstructive CAD (INOCA) can occur when there are structural or functional abnormalities of any part of the coronary vasculature – even the parts we can't see. Can coronary microvascular dysfunction (CMD) cause ischaemia? Until very recently the evidence-based properties of the coronary microcirculation could be summarised in a few sentences. It exists. It's important. It can become dysfunctional. Dysfunction is difficult to diagnose. Dysfunction is even more difficult to treat. Nonetheless, it is accepted that CMD is real, not at all uncommon, and has significant clinical consequences². Multiple studies have demonstrated that microvascular dysfunction is associated with an impaired quality of life, higher health-care utilisation and an increase in major adverse cardiac events (MACE)³. So, as we accept that the microcirculation exists, is important, and can become dysfunctional, we need to understand how it can be diagnosed and why it impacts clinical outcomes.

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In this issue of EuroIntervention, Vandeloos and colleagues report that in patients with an intermediate pretest probability of CAD, an invasive functional assessment using fractional flow reserve (FFR) for the epicardial circulation and the index of microcirculatory resistance (IMR) for the microcirculation led to a substantial improvement in the diagnostic performance of ETT-identified ischaemia⁴. In this multicentre study of 107 patients and 137 vessels, obstructive CAD (diameter stenosis [DS] >50% by quantitative coronary angiography [QCA]) was present in 39%, FFR ≤ 0.80 in 37%, and CMD (IMR ≥ 25) in 20% of patients. Critically, an FFR ≤ 0.80 and IMR ≥ 25 was present in only 3.7%, suggesting that for the vast majority of patients the ETT evidence of ischaemia could be clearly attributed either to epicardial disease or CMD. Using the false discovery rate (FDR) as the primary endpoint, they report the following important findings. First, compared to a QCA DS >50%, the addition of FFR did not reduce the FDR (60.7% vs 62.6%; $p=0.803$). These findings suggest that QCA and FFR do not identify different populations with a positive ETT. Second, the addition of the IMR to a QCA DS >50% or FFR ≤ 0.80 significantly reduced the FDR with the identical magnitude. These results confirm the findings that QCA and FFR have a similar yield on ETT, but more importantly, assessment of CMD using IMR is additive for “true positive” ischaemia.

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And so, here it begins again, macroconfusion about the coronary microcirculation⁵. The diagnosis of CMD is severely hampered by the lack of a uniform definition or accepted gold standard for diagnosis. The most commonly used index for the assessment of the microcirculation, both non-invasively and invasively, is the coronary flow reserve (CFR). At its most simplistic level, CFR evaluates the vasodilatory capacity of the microcirculation and, therefore, the ability of the microcirculation to appropriately increase myocardial blood flow. The major limitation of CFR is that it may also be impaired in the presence of significant epicardial obstruction, limiting its clinical utility to solely evaluate microvascular function non-invasively.

Even in the absence of obstructive coronary disease, the different methodologies used for invasive and non-invasive assessment of CFR have poor correlation^{6,7}. While it has been clearly established that low CFR is associated with a worse long-term clinical outcome, the mechanistic contribution of the microcirculation to this outcome is unclear⁸. Indeed previous studies have shown that the majority of patients with low CFR on non-invasive testing actually have low CFR because of an elevated resting flow⁹. It could be argued that this “functional CFR” is no different to metabolic equivalents of task (MET) in its ability to predict prognosis by simply identifying a high-risk group of sicker patients. In this regard, a recent study using PET CFR <2 to identify CMD found limited diagnostic utility of ETT to identify ischaemia¹⁰. This is an important distinction, as the current study used the IMR to evaluate CMD.

The IMR is a specific index of microvascular resistance, independent of haemodynamic changes, and more reproducible than

CFR¹¹. Limitations of the IMR include, a lack of an accepted normal or reference range, systematic differences of the IMR in different coronary arteries, lack of outcome data in chronic coronary syndromes and a poor correlation with CFR⁷. The measurement of absolute microvascular resistance by continuous coronary thermodilution, which has recently become available for use in humans, may prove to be more accurate, precise, reproducible and agreeable with other modalities.

While the current report clearly indicates the additive value of IMR in improving the FDR of ETT detection of ischaemia, many questions remain. In the 67 patients with INOCA, the mean IMR (21.2 \pm 12.8) and CFR (3.0 \pm 2.2) were normal. Would true CMD not be a low CFR and high IMR (i.e., reduced flow because of increased microvascular resistance)? No assessment of improvement in the FDR is presented for either CFR alone or the combination of CFR and IMR, both of which have prognostic implications². Further, CMD was present in only 27% of patients with INOCA, suggesting that despite the improved FDR for ETT-detected ischaemia using IMR, the dreaded false positive stress test continues to hamper the diagnostic utility of ETT. Also, because patients with a negative ETT were not referred for coronary angiography, a classical analytical approach assessing diagnostic utility based on sensitivity, specificity, and accuracy was not possible.

INOCA has prompted a shift in thinking about what a positive test for ischaemia means. In the absence of obstructive CAD on anatomical imaging, rather than dismissing stress test results as false positives, the work by Vandeloos and colleagues supports a position where we instead consider the results to be true positives, prompting additional assessment for CMD. In this regard, ETT is a simple and well-established test which may reduce, but not eliminate, our macroconfusion about the coronary microcirculation.

Conflict of interest statement

Z.A. Ali reports institutional research grants to St Francis Hospital from Abbott, Philips, Boston Scientific, Abiomed, ACIST Medical, Medtronic, and Cardiovascular Systems Inc.; is a consultant to Amgen, AstraZeneca, and Boston Scientific; and has equity in Shockwave Medical. A. Jeremias reports institutional funding (unrestricted education grant) from Philips/Volcano and is a consultant for Philips/Volcano, Abbott Vascular, ACIST Medical, and Boston Scientific.

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