Risk stratification of patients with normal myocardial perfusion imaging: help comes from the periphery

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This editorial refers to ‘Value of reserve pulse pressure in improving the risk stratification of patients with normal myocardial perfusion imaging’†, by D. Thomas et al., on page 2074

Nuclear imaging has an established clinical role in the non-invasive diagnosis of coronary artery disease (CAD), allowing accurate patient stratification and allocation to the best form of treatment. Semi-quantitative assessment of regional myocardial perfusion with single-photon emission computed tomography (SPECT) is a non-invasive, robust, and widely available method of assessing myocardial ischaemia and has a well established role in the clinical setting. One of the recognized strengths of SPECT perfusion imaging is its very high negative prognostic value. The annual rate of death and non-fatal myocardial infarction in patients with normal stress SPECT perfusion imaging is \( < 1\% \) per annum, i.e. similar to that in the general population.¹

A recent retrospective study by Rozanski et al.² reports a decline in the frequency of abnormal perfusion detected by stress myocardial perfusion imaging (MPI) with SPECT in North America over the last two decades. The frequency of an abnormal myocardial perfusion image is now very low in patients able to exercise without typical angina. These findings highlight the need for developing cost-effective diagnostic algorithms for symptomatic patients who are at low risk and do not show inducible myocardial ischaemia during MPI. On the other hand, a normal myocardial perfusion image is not the equivalent of a normal coronary circulation: diffuse atherosclerosis, balanced ischaemia, and microvascular dysfunction hamper the increase of myocardial blood flow during exercise without showing localized perfusion defects.

Histopathology studies have shown that atherosclerosis is diffuse in nature, and in symptomatic patients chest pain is often considered non-coronary because no single focal stenosis is found at angiography. Recent evidence indicates that patients with normal stress MPI findings are not a homogeneous group. In fact, it is common knowledge that decreased perfusion tracer uptake in MPI is based on induction of flow heterogeneities due to flow-limiting stenoses, whereas segments with the quantitatively highest tracer uptake are considered the reference region with supposedly normal perfusion. The latter reference regions, however, may also be subtended by a diseased coronary artery, decreasing the sensitivity of MPI and explaining why, in one study, only 29% of patients with three-vessel disease had defects in all three coronary territories.³ In line with this, a recent study by Fiechter et al.⁴ using positron emission tomography has demonstrated that 33% of patients with normal MPI findings were correctly re-classified as having abnormal findings when full quantification of myocardial blood flow and flow reserve were added. Similar results have been reported in other studies in patients with CAD where the addition of absolute flow quantification and flow reserve identified subgroups of patients at higher risk of serious adverse events.⁵,⁶ However, these corrections cannot be applied to substratify patients undergoing SPECT perfusion studies due to the technical limitations that do not allow measurement of absolute myocardial blood flow and flow reserve with this technique.⁷

Thomas et al. have now examined exercise SPECT-MPI in a large cohort of 4269 consecutive symptomatic patients without known CAD and normal or mildly abnormal MPI results (summed stress score \( \leq 3 \)).⁸ To complement MPI and improve patient stratification, they propose a new method, based on the changes in arterial pulse pressure from rest to exercise. The peak exercise and reserve-pulse pressure (arithmetic difference of rest and peak exercise pulse pressure) identify the lowest risk patients, and add prognostic value to conventional risk markers such as Duke treadmill score (DTS), heart rate recovery

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and diastolic time intervals, and peripheral vascular resistance; it can be simplified as the ratio of end-systolic pressure (ESP) to stroke volume (SV) (Figure 1). The performance of the LV can be calculated from the pressure–volume loop as end-systolic elastance \( E_{\text{LV}} \). The latter value is inversely related to the ejection fraction (EF), with the advantage of discriminating between alterations intrinsic to the LV or in the arterial tree. Increases in \( E_{\text{LV}} \) indicate an increase of myocardial contractility, whereas increases in \( E_{A} \) reflect a more complex physiological or pathological response. The normal response during exercise is an increase in \( E_{A} \) and a larger increase in \( E_{LV} \), resulting in a decrease in the ratio \( E_{A}/E_{LV} \). In older subjects, the increase in the \( E_{LV} \) component is less marked. In patients with systolic heart failure, \( E_{A} \) is elevated at rest with a depressed \( E_{LV} \). \( E_{A} \), \( E_{LV} \), and \( E_{LV}/E_{LV} \) do not change with exercise, indicating an impairment in both arterial and LV elastance reserves. The picture is more complex, and fewer data are available, in those patients, mainly hypertensive females, with heart failure and preserved EF (HFpEF). These patients have a high \( E_{A} \) and \( E_{LV} \) at rest and a severely blunted \( E_{LV}/E_{LV} \) reserve with exercise, unmasking a pre-symptomatic HFpEF as recently reported in a small cohort of hypertensive females.

In the large study cohort of Thomas et al., reserve-pulse pressure proved a valuable predictor of all-cause mortality; such an approach, however, will be limited to the subset of patients suitable for exercise stress, an ever-shrinking proportion of patients because of increasing age and expanding use of pharmacological stress which is easier to perform. Earlier this year, Suparwila et al. reported that in addition to cardiovascular risk factor burden, long-term risk varies quite substantially depending on the stressor in patients with normal MPI. The annualized mortality event rate was 0.8% per year in patients able to exercise, whereas in patients with normal pharmacological MPI and \( \geq 2 \) significant CAD risk factors, there was a five-fold increase.

Moreover, the use of medications that hamper chronotropism or inotropism can be a confounding factor that has not been fully elucidated by the study by Thomas et al.

Will this addition to MPI prove useful in the clinical arena? Its greatest merit is that it is simple to obtain and at no extra cost. Nevertheless, we feel that there is still room for refinement. Current softwares calculate ESV and SV from gated blood pool, and calculating ESP as \( 0.9 \times \) systolic blood pressure is straightforward; thus, it would be very easy to estimate arterial–ventricular coupling. We encourage Thomas et al. to exploit fully the wealth of their data, adding a more mechanistic insight, at least in a subset of selected patients.

Conflict of interest: none declared.


