

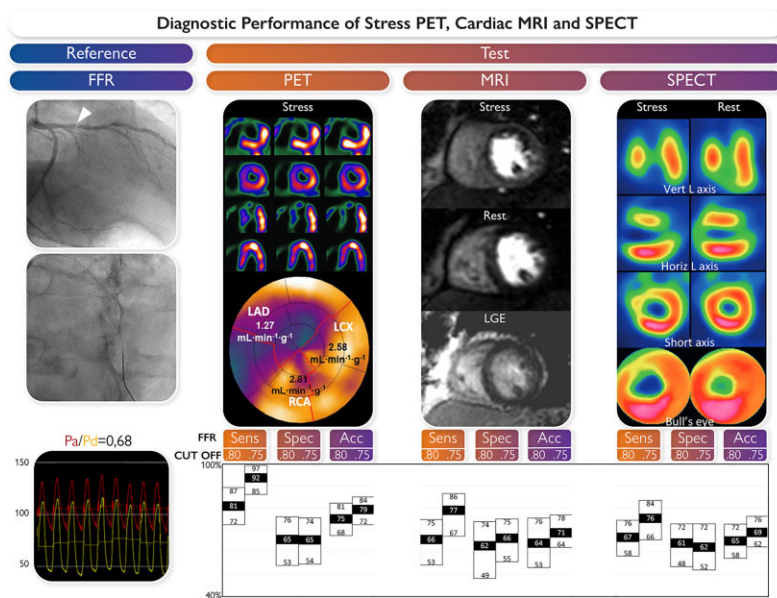
Stress imaging versus fractional flow reserve: what comes first—the chicken or the egg?

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This editorial refers to ‘Functional stress imaging to predict abnormal coronary fractional flow reserve: the PACIFIC 2 study’, by R.S. Driessen *et al.*, <https://doi.org/10.1093/eurheartj/ehac286>.

Graphical Abstract



Performance of positron emission tomography (PET), magnetic resonance imaging (MRI), and single-photon emission computed tomography (SPECT) for diagnosing fractional flow reserve (FFR)-defined significant coronary artery disease (CAD) on a per-patient level. A 67-year-old male who underwent multiple diagnostic tests because of stable angina serves as a graphical summary of the PACIFIC 2 study (Driessen *et al.*³). The final diagnosis is made using invasive catheter coronary angiography that showed a significant stenosis of the mid-portion of the left descending artery (left panel, arrowhead). After insertion of a pressure wire, the pressures distal (Pd) to the stenosis and in the aorta (Pa) were recorded under hyperaemia, and the FFR (Pa/Pd) was 0.68, which was consistent with a significant flow reduction, and perfectly correlated with the anteroseptal perfusion defects on stress PET (middle left panel), MRI (middle right panel), and SPECT (right panel). These defects were reversible, as both resting MRI and SPECT perfusion showed no defect. Furthermore, there was no scar on late gadolinium-enhanced (LGE) MRI. The lower part of the figure reports the respective diagnostic values (sensitivity, specificity, and accuracy) of these tests in the PACIFIC 2 study for FFR-defined significant coronary artery disease (i.e. either $FFR \leq 0.80$ or $FFR \leq 0.75$) in symptomatic patients with prior myocardial infarction and/or percutaneous coronary intervention on a per-patient basis.

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Ischaemia testing helps in risk stratifying patients and guiding treatment strategy, with non-invasive testing being the preferred diagnostic strategy in patients with high clinical likelihood, in whom revascularization after failed medical therapy is likely, based on the 2019 ESC guidelines.¹ With regards to the choice of non-invasive ischaemia testing, both the ESC and AHA/ACC guidelines give equal weighting to all stress imaging modalities, i.e. cardiac positron emission tomography (PET), magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), and echocardiography, for the diagnosis of myocardial ischaemia in patients with chest pain despite optimal guideline-directed medical therapy.^{1,2}

Meanwhile, the 2021 AHA/ACC guidelines recommend invasive fractional flow reserve (FFR) in patients with no prior stress testing, who are referred for invasive coronary angiogram (Class I, Level of Evidence A), while the 2019 ESC guidelines recommend FFR in patients with inconclusive or conflicting results from non-invasive testing during invasive coronary angiogram (Class IIa, Level of Evidence B).¹ Invasive FFR was designed to enable a swift on-table revascularization decision based on the haemodynamic significance of epicardial coronary artery stenosis. However, its role has evolved and gradually risen to be the reference standard that non-invasive stress testing is often compared against, a role probably driven by our collective enthusiasm for comparison and simplification. The numerous comparative studies in the literature reflect our interest in knowing how the diagnostic performance of any given test measures up against its counterparts and, ultimately, against an arbiter that confirms or refutes the validity of other test results.

Reported in this issue of the *European Heart Journal*, PACIFIC 2 is a prospective, single-centre study that compared the diagnostic performance of quantitative stress PET with [¹⁵O]water and both qualitative stress–rest cardiac MRI and ^{99m}Tc-tetrofosmin SPECT in patients with established coronary artery disease (CAD), using invasive FFR as the standard of reference.³ Ninety percent of the cohort had a prior percutaneous coronary intervention (PCI), while 53% had a prior myocardial infarction (MI). PET had the highest sensitivity (81% vs. SPECT 67% and MRI 66%) for diagnosing haemodynamically significant (FFR ≤ 0.80) CAD, while the specificities for all three imaging modalities were similar. Although the differences in accuracy were not statistically significant among the imaging modalities, it was numerically higher with quantitative PET (75%), followed by qualitative SPECT (65%) and stress cardiac MRI (64%).

Although the imaging modalities being compared are all perfusion based, each has its strengths and limitations, which might account for the differences in performance matrices. PET allows for quantitative myocardial blood flow (MBF), which has been shown to identify multivessel disease and quantify the extent of ischaemia more accurately than visual analysis of perfusion imaging.⁴ Quantification of absolute MBF with PET also reduces false-negative scans due to balanced ischaemia and enables detection of patients with microvascular dysfunction, in whom the stress–rest perfusion imaging could appear normal.⁵ SPECT is the most widely used perfusion imaging technique among the three, but has the lowest spatial resolution. This study adopted qualitative (visual) SPECT and MRI techniques for perfusion assessment and made head-to-head comparison with quantitative PET, a strategy that the authors rightfully acknowledged as a limitation. The choice of qualitative over quantitative assessment of MRI stress perfusion might account for its lower diagnostic value.

Indeed, the study has shown that quantitative MRI perfusion is superior to visual assessment at defining the extent of ischaemia in multivessel disease.⁶ In addition, quantitative perfusion MRI has been shown to accurately detect haemodynamically significant epicardial stenosis and distinguish microvascular dysfunction from three-vessel disease.⁷

The diagnostic performance indices in PACIFIC 2 were considerably lower compared with previous meta-analyses conducted in patients with suspected or known CAD.^{8,9} This might be accounted for by the study cohort that was comprised of patients with prior CAD and the unique physiological changes post-MI or post-PCI. FFR could be falsely elevated post-MI when the microvasculature is damaged, resulting in underestimation of the severity of epicardial stenosis. The reason for this is that the FFR value is dependent on the amount of subtended myocardial mass, which has an inverse relationship with microvascular resistance, i.e. a lesser subtended myocardial mass means a lower number of parallel pathways through the microcirculation, resulting in higher microvascular resistance and higher FFR values for any given stenosis.¹⁰ Consequently, the lower specificity of stress testing (increase in 'false' positives) might be attributed to an inflated FFR reference standard.

The PACIFIC 2 investigators presented the diagnostic performance of stress testing using both FFR ≤ 0.8 and FFR ≤ 0.75 as reference standards, as FFR values in between these cusps represent a grey zone with questionable value in determining the need for revascularization in post-MI/PCI cohorts.¹¹ Statistically, lowering the FFR cut-off increases the sensitivity of stress testing. Using a lower FFR cut-off value of 0.70, the sensitivity improves whereas the specificity remains $< 65\%$ across all modalities, which means up to a third of patients would have had false-positive stress tests (SPECT sensitivity 82%, specificity 61%; PET sensitivity 99%, specificity 62%; MRI sensitivity 79%, specificity 65%, based on data from their supplementary table S1). Whether the stress test results were false positive (using FFR as reference standard) or, conversely, the FFR results were false negative (using the stress test as reference standard) is another intriguing insight yet to be investigated. In the context of PACIFIC 2, the false-positive stress tests could be that underlying coronary microvascular dysfunction (CMD), which can be present with or without haemodynamically significant CAD,¹² considerably impacts raw non-invasive myocardial perfusion techniques, whereas FFR avoids these confounding effects by dividing the mean intravascular pressure distal to a coronary stenosis by the mean pressure in the aorta. A considerable proportion of the PACIFIC 2 study cohort had cardiometabolic syndrome, which predisposes them to CMD. The mean body mass index of the study population was 27.4 kg/m², which is in the overweight range, 65% were hypertensive, 41% had smoking history, and 21% were diabetic.

Perhaps the most fundamental question here would be whether benchmarking stress testing against invasive FFR is fair or, more importantly, meaningful. In other words, should detection of FFR-defined haemodynamically significant epicardial stenosis be the holy grail of non-invasive stress testing? Revisiting the history of FFR might help us get closer to the answer and if not, provide us with some food for thought at least. The first-in-human FFR study was conducted in 1994, when FFR was validated against [¹⁵O]H₂O PET.¹³ The FFR cut-off value of 0.75 was derived from a subsequent comparative study against stress testing, i.e. bicycle exercise testing,

thallium scintigraphy, and dobutamine stress echocardiography, in 1996.¹⁴ Comparison between raw non-invasive stress testing and FFR thus operated on a circular logic, leading us to a position mirroring where we started from almost three decades ago. One possible way out of this catch-22 situation is perhaps to abandon the idea of a gold standard altogether. Instead of searching for the one elusive test that trumps all, recognize that all coronary physiological tests have their own niche and work towards integrating various, sometimes discrepant, test results for the best clinical outcomes.

The choice of stress testing should be individualized according to the patient's risk profile, the clinical question, and local availability. In general, stress perfusion modalities with blood flow quantification correlate most closely with invasive FFR, even more so when the non-invasive stress perfusion values are normalized (i.e. divided by the same value in a distant area).^{8,9,15} Adding to the complexity is the presence of prior MI or revascularization, which poses technical challenges to perfusion stress interpretation, especially visual-based assessment, and adds nuances to the interpretation of invasive FFR. Beyond the technical and physiological separation between stress tests, one ought to be cognizant that ischaemia exists in a continuum. Dichotomizing ischaemia, whether using a certain FFR cut-off or MBF cut-offs is no doubt convenient, widely accepted, but inherently flawed.

In summary, the authors of the PACIFIC 2 study should be commended for adding an important, well thought out, and eloquent piece of literature to the field of multimodality stress testing. Because of the conceptual and technical limitations of comparing stress testing with invasive FFR (or vice versa), their study results were somewhat 'negative' in the sense that non-invasive stress perfusion tests failed to accurately predict FFR-defined haemodynamically significant CAD in patients with prior MI/PCI. The bigger picture nevertheless suggests that none of the coronary physiological testing methods surpasses the others. We should thus work towards creating an inclusive environment that encourages integration, collaboration, and open communication between the imagers, interventionists, and the ordering physicians.

Conflict of interest: none declared.

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