The assessment of ischaemic burden: thoughts on definition and quantification

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The most recent guidelines recommend some proof of ischaemia before invasive angiography or revascularization.1 This is based on multiple outcome studies, mainly from SPECT perfusion imaging,2 but also from stress echocardiography,3 or cardiovascular magnetic resonance (CMR) imaging either using adenosine stress first pass perfusion or dobutamine stress wall motion analysis.4,5 The majority of these studies show that patients without ischaemia have an excellent prognosis, while those with some grade of ischaemia have more events. Using invasive pressure measurements in the coronary arteries (FFR) to guide revascularization has convincingly demonstrated that patients without proof of ischaemia should not be revascularized.6

There is less data on the benefit of revascularizing patients with ischaemia, but there is increasing evidence that patients should be guided by the amount, rather than the pure presence of ischaemia.7

Most of these data stems from SPECT studies either assessing outcome from retrospective data or subgroup analyses in prospective trials. There is no prospective randomized trial assessing the amount of ischaemia a patient can tolerate without increasing the likelihood for a cardiac event or prospective randomized data on the benefit of revascularization in stable angina.

Thus, the assessment and quantification of ischaemic burden, rather than the pure detection of myocardial ischaemia, is the next important step towards optimizing therapy strategies in patients with coronary artery disease.

In the current issue of the European Heart Journal of Cardiovascular Imaging, Motwani et al. examined 35 patients with angiographic triple vessel disease (VD) (stenosis >75%), 35 patients with normal coronary arteries and 35 patients with 1–2 VD with two CMR stress/rest perfusion scans. One scan was performed with a standard resolution of 2.5 mm in-plane and a contrast dose of 0.05 mmol/kg body weight Magnevist, the other with a high resolution of 1.6 mm in-plane and a contrast agent dose of 0.1 mmol/kg body weight. In patients with 3VD the authors find significantly more abnormal segments and territories with the high-resolution/high-contrast agent scan and a higher ‘ischaemic burden’ in comparison to the standard resolution/low contrast-agent scan. In 57% of patients with angiographic 3VD, they found ischaemia in three territories by high resolution and 29% by standard resolution imaging. The authors conclude that high-resolution perfusion CMR may be preferred for risk stratification and management of patients with angiographic 3VD.

The authors can be congratulated for addressing the topic of measuring ischaemic burden in patients with multivessel disease and performing two CMR studies in the same patients. The results clearly demonstrate that different imaging methods result in dramatically varying results when extracting ‘ischaemic burden’. If the change of spatial resolution and contrast agent dose within ONE imaging modality changes the results to such an extent, it may be worth to reconsider some aspects of ‘ischaemic burden’.

How is ischemic burden defined?
How much quantification is required?
What is the best reference standard?
How can it be validated?
What is the best imaging method?

The definition of ischaemic burden remains unclear. Each modality uses different criteria, most of which as somewhat visual or semiquantitative at the most, such as ‘number of segments with new or worsening wall motion abnormality’ for stress echo or dobutamine stress MR, the ‘summed stress score’ or ‘total perfusion deficit’ for SPECT imaging or the number and transmurality of ‘perfusion defects’ for CMR. From pathophysiological considerations, one would expect different scores for the different measures to describe the same ischemic defect (e.g. since perfusion defects precede wall motion abnormalities, a smaller number of segments with inducible wall motion abnormality in comparison to inducible perfusion defects). The relation of extent to severity or the relative importance of transmural to circumferential abnormalities has not been studied in detail. However, we do know that larger perfusion defects or areas with inducible wall motion abnormalities confer a worse prognosis than smaller defects. In a recent publication, Shaw et al. have reviewed the literature and related the various measures of ischaemic burden to outcome for different modalities.7 The difficulties to define clear cut-off values are highlighted by the results from the paper from Motwani et al.

Potentially full quantification (blood flow in mL/g tissue/min) may help us to better define ischaemic burden and SPECT and CMR are
joining PET in the ability to determine absolute blood flow.\(^8,9\) However, even then, the relationships of extent vs. severity will remain a difficult research topic. Research is further complicated by the lack of a reference standard. While FFR has been shown to improve outcome if used to guide revascularization,\(^6,10\) the main finding of the DEFER and FAME study was that patients without ANY ischaemia should not be revascularized, as such, it did not provide data on the relation between ischaemic burden and outcome. While outcome studies, such as the ISCHEMIA (http://clinicaltrials.gov/show/NCT01471522) or the MR-INFORM trial,\(^11\) will help us to better understand how to optimally guide patients with stable chest pain and myocardial ischaemia it remains important to remember that we do not only strive to improve outcome but also the quality of life and provide further management on clinical management decisions. The current results provide us with some potential clues on avenues of science that can further develop strategies of care following index stress CMR to guide effective detection of high-risk patients. CMR has so many technical advantages with tremendous progress made over the last decade which can revolutionize the diagnosis of cardiovascular disorders in millions of patients. The key will be to translate the distinct imaging advantages into effective strategies of care that directly improve the quantity and quality of our patient’s lives.

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