

EDITORIAL COMMENT

The Trials and Tribulations of Conducting Stress CMR Quantitative Analysis Studies*



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In the last few years, there have been major advances in stress perfusion cardiovascular magnetic resonance (CMR) toward automatic quantification (1). Quantitative analysis (QA) promises a wide range of benefits particularly by making interpretation of images simpler, faster, and less susceptible to reader experience. In this issue of *iJACC*, the study by Kotecha et al. (2), was designed to compare the diagnostic accuracy of CMR quantitative perfusion mapping to visual assessment of first-pass perfusion images in detection of multivessel coronary artery disease (CAD).

In this retrospective study, a total of 151 patients had undergone both stress CMR and invasive coronary angiography (CA) within 6 months of each other. Stress CMR was assessed by both perfusion mapping QA and by visual analysis. CAD was defined as angiographic stenosis of $>90\%$ by visual assessment or by fractional flow reserve (FFR) of <0.80 for intermediate 50% to 90% stenosis. The study found QA to be superior to visual assessment in identifying the extent of CAD via better detection of ischemic burden and coronary perfusion territories in multivessel CAD.

Although this is a well-done and significant study for advancing the field of stress CMR, it is important to consider the challenges faced in performing such a study.

In designing studies that assess the accuracy of stress tests, one has to determine a gold standard,

which has typically been CA. More recently, FFR has been used due to the better physiological assessment than the visual degree of stenosis. There are a number of challenges however, that need to be considered when using this gold standard. First, is determining the definition of positive CAD by CA beyond the degree of stenosis. Specifically, are all vessels included, or only vessels that meet a certain diameter cutoff (i.e., small secondary and tertiary vessels)? To include or exclude these vessels is not a straightforward decision, and it is unclear, in this study, if a cutoff for vessel size was used. Second, determining the degree of stenosis as positive for CAD is challenging because the physiological effect is not dichotomous. Although it is true that FFR is a major advance in addressing this limitation as it directly assesses the physiological impact of the visual stenosis, there are still some aspects that need consideration. For example, in this study, a visual assessment of 50% as a cutoff to pursue FFR was used. Although this is a reasonable cutoff, one should consider that the presence of a long 40% lesion or multiple tandem 40% stenosis could potentially be flow limiting, but would not be assessed by FFR. Third, the issue of ischemia at the tissue level from microvascular disease, but no significant obstruction at the epicardial level, is a challenging problem with no easy solution when designing these types of studies. Finally, there is the challenge of “matching” the perfusion territory on the stress test to the coronary artery territory on angiography. The authors decided to use the standard American Heart Association coronary artery distribution territories (3). However, this may lead to inaccuracies, particularly along the border coronary territories, as well as not accounting for individual variability of coronary artery distribution, which can be seen in close to 1 in 4 people (4,5). Hence, rather than assigning fixed territories for

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coronary arteries, a more vigorous method would be to assess the CA for each coronary artery territory and assign the territory to a 17-segment model by blinded reviewers, and then “match” this to the perfusion territory identified by the stress study (6). Although this method is more scientifically based, it still can be challenging in how a match is defined. Overall, even with these limitations in using CA plus FFR as the gold standard, the MR-INFORM (The Myocardial Perfusion CMR versus Angiography and FFR to Guide the Management of Patients with Stable Coronary Artery Disease) study showed that stress CMR was non-inferior when compared to FFR with respect to predicting major adverse cardiac events, establishing stress CMR as an alternative reference standard (7).

Another challenge in designing the accuracy of stress studies is defining a “positive” imaging study. In the MR-INFORM study, at least 2 segments were used to define clinically significant inducible ischemia (7). Kotecha et al. (2) used a similar definition. In the study cohort, 7.5% of the perfusion territories had only 1 ischemic segment, of which 29% were found to have obstructive stenosis. This is a very important issue clinically. Does an interpreter call a study negative if there is only 1 segment positive? If they call it negative, are they missing clinically relevant atherosclerotic disease that might benefit from medical therapy? One of the key values of a stress test is detecting the presence of obstructive coronary artery disease, not just the extent. To this point, an interesting finding in this study was that when visual analysis was compared with quantitative analysis for the detection of CAD, visual assessment had a higher sensitivity (92% vs. 84%, respectively).

Other considerations in the methodology of this study include:

1. As this novel quantitative technique is being developed and optimized, the CMR readers in this study had a role in manually excluding artifacts (via visual assessment) from the regions of interest. Improving artifact detection would be an important consideration for future standardization of the technique to allow for the potential of complete automation with artificial intelligence. To achieve that, the definition and burden of such image artifacts should be clarified.
2. It is important to take into account rest perfusion images to differentiate true artifacts from

positive defects. An apparent perfusion defect seen with rest and stress may be a dark rim artifact, whereas one at stress only is more likely a true positive defect (8). The use of the rest imaging portion of the study was not clearly defined in this paper.

3. Including patients with known prior CAD and/or myocardial infarction can affect the accuracy of the perfusion studies. Known prior infarcts included in investigations to predict CAD can cause referral bias and inappropriately raise sensitivity and specificity (9).

We raise these challenges with designing stress tests not to diminish the important findings of the study by Kotecha et al. (2), but rather as considerations to ponder when evaluating studies that try to determine the accuracy of stress tests. In fact, we agree with the authors’ proposal that visual analysis can underestimate ischemic burden due to the relative differences of perfusion defects (i.e., a mildly severe perfusion defect might be “obscured visually” by an adjacent severe perfusion defect), whereas objective measurements can be obtained with QA that are not prejudicial to these visual challenges. With the addition of automated pixelwise quantification, detailed and complete assessment of myocardial ischemia could be improved.

Quantitative applications are becoming exceedingly prominent in the published medical data and the field of cardiac imaging. More work is to be done, but this study certainly brings us one step closer to the future of using artificial intelligence in CMR perfusion imaging, which is exceptionally promising. In conclusion, although there are methodological challenges to consider when evaluating all stress imaging studies, the study by Kotecha et al. (2) is sound and helps advance the field for utilizing quantitative assessment in determining the extent of CAD.

AUTHOR DISCLOSURES

Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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REFERENCES

1. Dewey M, Siebes M, Kachelriess M, et al. Clinical quantitative cardiac imaging for the assessment of myocardial ischaemia. *Nat Rev Cardiol* 2020;17:427–50.
2. Kotecha T, Chacko L, Chehab O, et al. Assessment of multivessel coronary artery disease using cardiovascular magnetic resonance pixelwise quantitative perfusion mapping. *J Am Coll Cardiol Img* 2020;13:2546–57.
3. Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart. A statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation* 2002;105:539–42.
4. Le MTP, Zarinabad N, D'Angelo T, et al. Sub-segmental quantification of single (stress)-pass perfusion CMR improves the diagnostic accuracy for detection of obstructive coronary artery disease. *J Cardiovasc Mag Res* 2020;22:14.
5. Ortiz-Perez JT, Rodriguez J, Meyers SN, Lee DC, Davidson C, Wu E. Correspondence between the 17-segment model and coronary arterial anatomy using contrast-enhanced cardiac magnetic resonance imaging. *J Am Coll Cardiol Img* 2008;1:282–93.
6. Heitner JF, Senthikumar A, Harrison JK, et al. Identifying the infarct-related artery in patients with non-ST-segment-elevation myocardial infarction. *Circ Cardiovasc Interv* 2019;12:e007305.
7. Nagel E, Greenwood JP, McCann GP, et al. Magnetic resonance perfusion or fractional flow reserve in coronary disease. *N Engl J Med* 2019;380:2418–28.
8. Schulz-Menger J, Bluemke DA, Bremerich J, et al. Standardized image interpretation and post processing in cardiovascular magnetic resonance: Society for Cardiovascular Magnetic Resonance (SCMR) board of Trustees Task Force on Standardized Post Processing. *J Cardiovasc Mag Res* 2013;15:35.
9. Cecil MP, Kosinski AS, Jones MT, et al. The importance of work-up (verification) bias correction in assessing the accuracy of SPECT thallium-201 testing for the diagnosis of coronary artery disease. *J Clin Epidemiol* 1996;49:735–42.

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