Diagnosis of diffuse ischemia with SPECT relative perfusion imaging: How to eat soup with a fork?

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EDITORIAL

Ever since Barry Zaret and colleagues first demonstrated stress-induced coronary ischemia using a rectilinear scanner and ^{43} K,[1] nuclear myocardial perfusion imaging (MPI) has relied primarily on detecting regional differences between normally and abnormally perfused myocardium to demonstrate ischemia. While the diagnostic and prognostic value of relative perfusion imaging has been well established for decades, it has also long been recognized that diffuse ischemia is more difficult to recognize and can be missed entirely when all coronary territories are somewhat equally affected, either due to multivessel obstructive coronary disease (balanced ischemia), or due to diffuse microvascular disease. Surrogate markers of balanced ischemia like transient ischemic dilation (TID) or a decline in left ventricular ejection fraction (LVEF) post stress can modestly improve the sensitivity for detection of multivessel coronary artery disease (CAD).[2,3] However, the ability for SPECT to detect left main or proximal three vessel CAD remains suboptimal with even modern SPECT techniques reported to have a sensitivity of 59%.[4] At the same time, microvascular disease is an important contributor to ischemic heart disease, especially in women,[5] and is often diffuse, thus remaining undetected on traditional relative MPI.[6]

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In this issue, Almuwaqqat et al. analyze differences between rest and stress SPECT count profiles and propose using this approach to quantify diffuse ischemia.[7] They describe the association between ischemia during mental stress and clinical outcomes in 300 patients with recent myocardial infarction enrolled in the Myocardial Infarction and Mental Stress Study 2 between 2011 and 2016. To detect and measure ischemia, they analyzed data from rest-stress Tc99m perfusion SPECT studies. They sought to overcome the limitations of relative SPECT perfusion imaging by quantifying per-segment differences in count profiles at stress and rest and comparing subjects exposed to mental stress with a reference population. This approach is a modification of a previously reported method.[8] The authors used the resulting cumulative score, termed X, as a measure of diffuse ischemia induced by mental stress (dMSI). Their main finding is that dMSI predicted adverse cardiac events. In addition, this was seen in women but not in men, and it persisted even when adjusting for regional ischemia as assessed conventionally, with semi-quantitative scoring of per-segment uptake.

Thus, by using a nonparametric analysis of count profiles derived from static SPECT acquisitions, the authors have found a novel method to quantify diffuse ischemia. Or have they?

In a landmark paper, Fryback and Thorbury proposed a hierarchical process of validation for clinical testing evolving from technical quality to diagnostic accuracy, including sensitivity and specificity, to impacts on clinical and therapeutic management, to outcomes benefit and finally cost-effectiveness.[9] This provides a framework for evaluating novel approaches in SPECT imaging. Indeed, several quantitative approaches to SPECT image analysis have been developed and validated over the years and they assess regional

ischemia and total ischemic burden with varying degrees of granularity.[10] Large observational datasets have linked the degree of ischemia measured with these methods to clinical outcomes.[11] Similarly, the authors of the present study demonstrated an association of their cumulative count difference score with clinical outcomes. However, that does not validate their approach as a way to quantify diffuse ischemia. To establish the diagnostic accuracy of a novel approach for assessing diffuse rather than regional ischemia, comparison with a gold standard or with validated methods would be needed.

Fundamentally, any analysis that endeavors to measure ischemia by comparing normalized stress and rest counts is still subject to the limitations of relative myocardial perfusion imaging. Therefore, no true quantification of total inducible ischemia and especially of diffuse or balanced ischemia appears possible. This is the Achilles Heel of not only this most recent proposed method, but of all nuclear SPECT analyses that aim to quantify ischemic burden based on normalized counts. To add a metaphor, using relative MPI to quantify diffuse ischemia is a little like trying to eat soup with a fork.

By contrast, there exists a substantial array of spoons—validated methods for measuring absolute myocardial blood flow. Quantification of myocardial blood flow with dynamic positron emission tomography (PET) imaging has extensive technical and diagnostic validation spanning over twenty years in clinical practice.[12,13] As noted by Venkatesh Murthy et al., evaluation of myocardial flow reserve (MFR) by PET would reclassify fully 34.8% of patients deemed intermediate-risk based upon risk factors and and qualitative perfusion.[14] Moreover several groups have demonstrated the cost-effectiveness of quantitative PET due to the added diagnostic value and ability to reduce false negatives from balanced ischemia as well as diagnose coronary microvascular dysfunction.[15] Because of the robust validation and cost-effectiveness of quantitative PET myocardial blood flow (MBF), the most recent AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR Guideline for the Evaluation and Diagnosis of Chest Pain suggested that PET MBF may be considered for the evaluation of chest pain with a class IIA, Level of Evidence B-NR recommendation.[16]

Although quantitative perfusion by cardiac MRI (CMR) has experienced less extensive clinical application relative to PET, its development as a clinical test can serve as another example of Fryback and Thorbury's hierarchical process of validation. Quantitative CMR has been tested in animal studies of microspheres[17] as well as by direct comparison with the other validated method, PET absolute blood flow quantification.[18] It could be demonstrated that CMR strongly correlates with a gold standard reference of O-15 water PET, with r-values ranging from $r = 0.81$ to $r = 0.91$, depending upon deconvolution model. CMR tends to slightly underestimate MBF relative to PET, although this cancels out when considering myocardial flow reserve (MFR), since it affects both rest and stress MBF.[18] CMR and PET have the highest accuracy of alternative non-invasive cardiac tests versus invasive angiography[19] and coronary physiology.[20] Modeling of stress CMR registry data has demonstrated cost-effectiveness versus invasive evaluation[21] and the Cardiovascular Magnetic Resonance and Single-photon Emission Computed Tomography for diagnosis of coronary heart disease (CE-MARC).trial demonstrated cost-effectiveness of CMR versus SPECT.[22] For these reasons, the Chest Pain Guideline also recommends CMR for the evaluation of quantitative MBF.[16] In the USA the uptake of CMR perfusion is reduced due to technical complexity and the lack of an FDA approved sequence and software post-processing tool, but this may change in the near future.

While PET and CMR currently garner the most contemporary clinical interest for non-invasive evaluation of MBF, other possibilities exist. One attractive option would be to add stress perfusion imaging to coronary CT angiography. Indeed, this remains an option but clinicians rarely employ CT perfusion due to higher radiation dose, difficult clinical workflow requiring time consuming physician oversight versus alternative imaging modalities, lacking US FDA approved post-processing tools, and significant artifacts on most clinically available scanners.[23] Nevertheless, the potential of a one-stop shop for coronary anatomy plus physiology remains an attractive consideration. In addition, echocardiography has validation to evaluate MBF either by Pulse Wave Doppler imaging of left anterior descending coronary artery or use of echo contrast agents to evaluate perfusion. Neither of these techniques has widespread clinical use at this time as they are technically challenging.

Using dynamic SPECT to measure absolute blood flow is appealing due to the widespread availability of SPECT, though it does rely on the responsiveness of modern CZT scanners. For technical validation, Wells et al.[24] demonstrated strong correlation of thallium and technetium SPECT with microspheres in a porcine model, MBF $r = 0.79$–90 and MFR $r = 0.62$–0.94 ($P < 0.01$). In a recent prospective trial, global MBF obtained with dynamic SPECT correlated well with PET when a spline-fitted reconstruction algorithm was used ($r = 0.81$, $p < 0.01$).[25] Overall, clinical implementation of quantitative SPECT is in the early stages, but the technology holds promise.

A method that reliably reflects diffuse ischemia in static SPECT images would enable much more widespread evaluation for this common problem because a large majority of cardiac nuclear imaging still relies on conventional SPECT cameras. One potential approach to quantify tracer uptake goes in this direction by using standard uptake values (SUV). The computation of SUV is used widely for non-cardiac and cardiac PET indications. However, while measuring SUV on non-dynamic quantitative myocardial SPECT appears theoretically feasible[26] and has been studied in resting images from a series of patients with multivessel coronary artery disease[27] there are barriers to its implementation for detecting ischemia, including inferior resolution and, thus far, lack of validation.

Overall, Almuwaqqat and colleagues are to be commended for applying a novel quantitative nuclear imaging method to a cohort of patients exposed to mental stress and establishing that ischemia predicted clinical outcomes. We cannot conclude that they were able to quantify diffuse ischemia because using relative MPI to detect and measure diffuse ischemia remains challenging. It is likely that non-dynamic SPECT is simply an inadequate tool for this, akin to eating soup with a fork. With quantitative PET and CMR, we have some solid spoons, and more are in development. Our dual challenges are to create high-quality evidence supporting new tools, and to to make the existing validated tools more broadly accessible.

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