Cardiovascular PET/MR: We need evidence, not hype

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Recent introduction of hybrid positron emission tomography/magnetic resonance (PET/MR) scanners has created excitement regarding potential applications in cardiovascular medicine. This has led to a number of optimistic assessments of its potential value in the nuclear cardiology literature, although most published data are still at the feasibility or pre-clinical level. Such excitement is understandable and provides “fuel” for generation of the necessary clinical validation studies, which will be required. Given the current scrutiny from payers and government agencies to reduce the costs of cardiac imaging, the responsibility for showing additive benefit lies on the shoulders of those advocating for new, more expensive technologies. In the case of PET/MR, this will be a major challenge, given the high costs of the hybrid procedure and the need for potentially harmful ionizing radiation compared to a cardiac magnetic resonance (CMR)-only approach. The aim of this editorial is to provide a critical appraisal of the current evidence base for clinical use of PET/MR in cardiology.

Key Words: Myocardial viability • Myocardial perfusion imaging: SPECT • Myocarditis • Myocardial perfusion imaging: PET • Magnetic resonance imaging

In a recent issue of the journal, Schindler and Schwaiger make the case for several applications of PET/MR in clinical cardiology.^{1,2} They argue that the simultaneous combination of molecular imaging PET tracers with high-resolution CMR imaging will improve the diagnostic accuracy and assessment of cardiovascular disease. The aim of this editorial is to provide a critical appraisal of this evidence.

Both CMR and PET can provide important diagnostic and prognostic information in patients with cardiovascular disease. However, given the costs of cardiac imaging, there is increasing pressure worldwide to show evidence for direct additive impact on clinical

care.^{3–5} Due to rising healthcare costs, appropriate use of cardiovascular imaging is under increasing scrutiny and emphasized by professional societies, third-party payers, and accreditation agencies.^{3–5} In this climate, the responsibility for showing additive benefit lies on the shoulders of those advocating for new, more expensive technologies. Moreover, given the potential harmful effects of exposure to ionizing radiation, the addition of PET to a CMR-only protocol needs to have compelling evidence-based benefits.

VIABILITY

Late gadolinium enhancement (LGE) using CMR has arguably emerged as the gold standard technique for imaging of myocardial scar and viability.^{6–8} The basic principle is inversion recovery imaging after a 5- to 10-minutes delay following intravenous administration of gadolinium contrast.⁹ With appropriate settings, normal myocardium appears nulled or black, whereas nonviable

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regions appear bright or enhanced. The mechanism underlying LGE is likely based on the inability of gadolinium chelates to cross intact cell membranes.¹⁰ In normal myocardium, myocytes are densely packed, and tissue volume is predominately intracellular (~75% to 80%). Therefore, the distribution volume of gadolinium is small, and tissue concentration is low in a typical “voxel” of normal myocardium. With acute necrosis (acute myocardial infarction, myocarditis, etc.), there is membrane rupture, which allows gadolinium to diffuse into myocytes. This results in increased gadolinium concentration, shortened T1 relaxation time, and consequent signal enhancement.¹¹ In the chronic setting, scar has replaced necrotic tissue, and the interstitial space is expanded. This again leads to increased gadolinium concentration and hyperenhancement.¹¹ In both acute and chronic settings, one can consider viable myocytes as actively excluding gadolinium contrast. Thus, the unifying mechanism of LGE appears to be the absence of viable myocytes rather than any inherent properties that are specific for acute necrosis, collagenous scar, or other forms of nonviable myocardium. LGE is the only imaging technique to have undergone multicenter validation to assess its ability to detect myocardial infarction.¹² Kim et al. scanned 282 patients with acute and 284 with chronic first-time myocardial infarction in 26 centers throughout the U.S., Europe, and South America. This multicenter study showed that the sensitivity of LGE reached 99% and 94% in acute and chronic myocardial infarction, respectively. In animal models, extensive comparisons have shown a nearly exact relationship between the size and shape of infarcted myocardium by LGE to that of histopathology.^{13,14}

In his editorial, Schindler argues that LGE may overestimate the scar region in patients with acute myocardial infarction.¹ However, he failed to comment on several recent PET/MR studies, which appear to show that the area of reduced FDG uptake largely overestimates the size of the infarct as described by LGE after acute myocardial infarction.^{15,16} Indeed, these studies seem to suggest that FDG uptake is reduced in reversibly injured myocardium and recovers over time.¹⁷ Schindler cites a small recent PET/MR study by Rischpler and colleagues in 28 patients imaged 5 to 7 days post percutaneous coronary intervention for acute myocardial infarction.¹⁸ He states that FDG uptake was a better predictor for functional recovery than segmental LGE transmural extent in some segments. However, the initial scans were performed after revascularization, which makes interpretation of these findings difficult.¹⁸ Indeed, the authors final conclusions in the Rischpler paper are that “there might be no additional value in the combination of both techniques—LGE and FDG PET”.¹⁸

Although future applications using novel molecular imaging tracers will certainly be of great interest, there is no evidence currently that the substitution of PET/MR over a CMR-only approach provides incremental clinical benefit in viability or infarct assessment—particularly given the additional cost and radiation burden that this would involve.

CARDIAC SARCOID AND MYOCARDITIS

The diagnosis of cardiac involvement from sarcoidosis can be difficult because the extent of disease is often limited and focal in nature. Postmortem studies have shown that patients with cardiac sarcoid frequently have lesions that are small and patchy, leaving much of the myocardium uninvolved.¹⁹ Multiple studies have shown that LGE can be used to determine cardiac involvement in patients with suspected cardiac sarcoid, and that this is associated with an adverse prognosis.^{20,21} A recent meta-analysis of 694 patients with suspected or confirmed cardiac sarcoid demonstrated that the annualized rate of either ventricular arrhythmia or death was 0.6% in LGE-negative patients compared with 8.8% in LGE positive patients.²¹ Similarly, a recent PET study showed that among 118 patients referred because of known or suspected cardiac sarcoid, those with abnormal perfusion and metabolism had a fourfold increase in the annualized rate of ventricular tachycardia or death.²² We believe these prognostic studies provide better guidance for decision-making than those cited by Schindler. Studies directly comparing PET and CMR for diagnosing cardiac sarcoid (including the ones cited by Schindler in his editorial) are currently extremely limited due to their small patient numbers, lack of statistical power, and inconsistencies in scan protocols.^{22,23} Moreover, these problems are compounded by a lack of a gold standard. Schindler suggests a unique role for PET in monitoring immunosuppressive treatment, but the standard used to assess effectiveness in the study that he quotes was left ventricular ejection fraction—which can be measured most accurately with CMR.²⁴ Schindler also incorrectly states that CMR LGE and T2-weighted sequences in combination fail to differentiate myocardial edema from myocyte necrosis. This assertion is inconsistent with substantial evidence in the medical literature and the experience of established CMR centers.²⁵ In addition, CMR T1 mapping-based quantitation of extracellular volume is a new validated tissue marker of fibrosis and may offer improved diagnostic accuracy.²⁶

Since sarcoidosis represents a form of myocarditis, many of the same principles apply to its diagnosis with CMR vs PET/MR. However, PET/MR data are limited to case reports only, and as Schindler admits in his

editorial, there are no systematic studies of PET/MR in myocarditis. In summary, although further studies exploring the utility of PET/MR in the diagnosis and management of cardiac sarcoid and myocarditis are of great interest, there are currently little data supporting such an approach—especially in the context of the additional cost and radiation burden that this would require.

IMAGING OF THE ATHEROSCLEROTIC PLAQUE

The ability to characterize atherosclerotic plaques and identify their vulnerability to rupture with noninvasive imaging has been a goal of researchers for many years.^{27,28} Currently, neither MR nor PET is used clinically for this purpose, although it is an active area of investigation. The use of novel molecular imaging tracers to interrogate the pathophysiology of atherosclerosis is certainly an attractive target. However, the small size and mobility of coronary artery plaques poses technical challenges related to co-registration of high-resolution MR images with the more limited spatial resolution of PET. In addition background, FDG uptake by myocardium remains an issue. Due to these difficulties, investigators have targeted the carotid circulation, which has the advantage of lack of movement and larger caliber vessels. However, to date, clinical PET/MR data have been limited to small feasibility studies showing structural and FDG uptake correlations in the carotid circulation.²⁹ These techniques may have future clinical applications in stroke management, but currently lack clinical evidence of incremental benefit. For now, they remain an exciting method for translational research.

CARDIAC MASSES

CMR is a powerful tool for assessment of cardiac masses and is widely used clinically for this indication. Combining the high resolution of cine imaging with tissue characterization capabilities, CMR provides a wealth of critical data in these cases. This includes information regarding vascularity, morphological features of local invasion, tissue characteristics, and functional consequences.^{30,31} CMR features demonstrate excellent accuracy for the differentiation of cardiac thrombi from tumors and can be helpful for the distinction of benign versus malignant neoplasms.^{30,31} To date, there is one published study on cardiac mass assessment by simultaneous 18F-FDG PET/MR imaging.³² Twenty patients with cardiac masses underwent integrated PET/MR imaging. Thirteen were found to be malignant and seven were benign. In this small cohort, there was high sensitivity and specificity in determining tumor malignancy but the stand-alone CMR already had

a similar high diagnostic accuracy. Thus, the incremental value of simultaneous PET/MR remains unclear. Moreover, pathology data were not available in ¼ of the patients, and the CMR protocol in this study was limited and did not include standard assessments such as rest perfusion imaging.

CONCLUSIONS

PET/MR offers the tantalizing promise of combining two powerful imaging modalities into one test with the hope that this will improve diagnosis of cardiovascular diseases. The technique certainly holds promise as a translational research tool to explore underlying mechanisms of disease. Although there are substantial theoretical advantages to this hybrid approach, there is currently no evidence to support incremental clinical benefit for diagnosis or management of cardiac disease. Given the current scrutiny from payers and government agencies to reduce the costs of cardiac imaging, this will be a major challenge for hybrid PET/MR since the costs of the hybrid procedure are high and there is need for potentially harmful ionizing radiation compared to a CMR-only approach. Moreover, the rapid development of novel CMR techniques will make this task increasingly challenging. However, this is an exciting and swiftly evolving area of investigation, and we hope that researchers in the field will arise to the challenge.

Disclosure

The authors declare that they have no conflict of interest.

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