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# PET/MR Imaging

## Current and Future Applications for Cardiovascular Disease



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### KEYWORDS

• Cardiac PET/MR hybrid imaging • [<sup>18</sup>F] Fluorodeoxyglucose • Myocardial perfusion stress tests

### KEY POINTS

- Combined PET/magnetic resonance (MR) systems are being developed and refined, with many commercially available systems now entering the market.
- Cardiac indications are potentially a fruitful area for this new technology, given how important PET and MR imaging each are in the workup and management of various cardiac diseases.
- Research to define the most effective use of this new hybrid technology is at a very early stage, although many preliminary studies have been promising.

### INTRODUCTION

Several different imaging modalities have been used to study the heart, each with strengths and weaknesses. Two advanced imaging modalities, magnetic resonance (MR) imaging and PET, have enjoyed decades of clinical use, each evolving to become integral to the management of certain cardiac patients.

MR imaging offers the ability to evaluate cardiac anatomy with high resolution and detailed tissue characterization. High temporal resolution cine image sequences have been developed, which capture high-resolution images of the heart throughout the cardiac cycle. Blood flow can be visualized and measured via velocity-encoded cine sequences. Postcontrast imaging adds an additional dimension, allowing for angiographic evaluation and assessment of early and late myocardial enhancement. Advanced MR

techniques continue to be developed, including MR spectroscopy and sequences capable of measuring myocardial strain, T1 mapping, and so forth. The full range of cardiac MR sequences, all providing targeted information, is available without the use of ionizing radiation.

Independently, PET has also become a modality ubiquitously used in cardiac imaging. Myocardial perfusion, historically evaluated via single-photon emission computed tomography (SPECT) tracers, can be assessed using PET agents. Rubidium-82 (Rb-82) and nitrogen-13 (N-13) ammonia allow for high-resolution imaging in a short acquisition time, and the possibility of quantitative measurements of coronary artery blood flow. These agents require an on-site generator or cyclotron, respectively, owing to the short half-life of these agents. Fluorine-18 [<sup>18</sup>F]-based perfusion agents, which have a longer half-life and can be transported

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over greater distances, are in late-stage clinical trials. An approved  $^{18}\text{F}$  perfusion agent could potentially result in PET replacing SPECT as the first-line modality for imaging myocardial perfusion.  $^{18}\text{F}$  tagged to glucose ( $^{18}\text{F}$ -fluorodeoxyglucose [FDG]) has been used to evaluate the myocardium in several settings, including conditions involving inflammation of the myocardium.

PET/computed tomography (CT) and SPECT/CT hybrid technologies have demonstrated the power of hybrid nuclear medicine imaging, with PET/CT in particular revolutionizing oncologic imaging. MR has several advantages over CT, making it potentially an excellent complement to the molecular information provided by PET, including excellent soft-tissue contrast, advanced functional techniques, and lack of ionization radiation. Combined PET/MR hybrid systems, however, have been an elusive technological goal until recently. MR imaging requires a bulky electromagnet and a plethora of electronics while PET cameras require a large array of sensitive detectors. The immense technological limitations of merging these technologies have finally been overcome in commercially viable scanners.

The clinical value of PET/MR as a hybrid technology has only limitedly been evaluated thus far. The published literature regarding this technology for cardiac indications, in particular, is somewhat limited. Cardiac indications would *prima facie* seem like a fruitful area, given the unique and complementary strengths of each modality individually.<sup>1,2</sup> In its simplest form, PET/MR could offer “one-stop shop” imaging modality for patients in whom PET and MR studies are separately indicated. For indications whereby acquiring both sets of images could theoretically be complementary, though not currently the standard of care, the new-found ease of acquiring both sets of images via hybrid scanners may result in a hybrid evaluation becoming the new standard. Finally, future research may determine ways to more deeply integrate the information obtained from each modality, resulting in new levels of diagnostic information.

This article reviews of the current state of PET/MR technology, followed by a brief overview of cardiac indications for which PET/MR may hold great promise.

## INSTRUMENTATION

Several technical challenges had to be overcome in designing commercially viable PET/MR imaging systems. A variety of solutions have been developed. The most straightforward solution, a

sequential system, involves the installation of a PET/CT scanner and an MR scanner adjacent to each other, in line, connected by a single patient table.<sup>3</sup> Sequential systems can also be installed with the 2 scanners in separate rooms, joined by a table system that spans the 2 rooms.<sup>4</sup> Both of these designs require relatively minimal changes to the underlying scanners, although they require large installation footprints. In addition, a truly simultaneous acquisition of PET and MR data is not possible.

The most integrated of the PET/MR designs is a concurrent system, in which the PET and MR components are physically combined in one scanner with a single gantry (Fig. 1).<sup>5</sup> This design involves a significant redesign of both the MR and PET hardware, most notably redesigning the MR hardware to make room for the PET and altering the PET detectors to become less sensitive to the MR scanner's magnetic fields. Fully integrated systems have smaller footprints, and allow for the simultaneous acquisition of PET and MR data. Simultaneous image acquisition allows for the most flexibility in designing optimal imaging studies.

PET/MR systems must have a mechanism to address attenuation correction, another major obstacle faced when developing these systems for clinical use. PET-only scanners and PET/CT systems use built-in radionuclide sources and CT, respectively, to create attenuation maps; neither technology is available in PET/MR



Fig. 1. A fully integrated PET/magnetic resonance system by General Electric Healthcare.

systems. Several methods to address attenuation correction have been studied including template-based methods,<sup>6–8</sup> atlas-based methods,<sup>6,9,10</sup> and approaches based on MR image segmentation,<sup>6,7,11–13</sup> and PET emission.<sup>14–16</sup> Future studies will likely determine which approach is the most optimal.

Hybrid PET studies are limited by patient motion. First, patient motion can result in misregistration between the anatomic and PET images. With potentially longer acquisition times, PET/MR may suffer from more misregistration issues in comparison with PET/CT. Second, patient motion can degrade the PET images themselves, given that PET images are acquired over multiple minutes per imaging bed. This limitation is particularly problematic when imaging the heart because of cardiac and respiratory motion, which can result in 4.9 to 9 mm of movement.<sup>17,18</sup> PET/MR systems, however, unlike PET/CT systems, have the potential to correct PET data for patient motion. Cine MR imaging can demonstrate the full range of cardiac and respiratory motion, thereby allowing for a map to be created that can be applied to the raw PET data to correct for motion.<sup>19</sup>

## CARDIAC TUMORS

The evaluation of cardiac tumors may be the most straightforward potential application of combined PET/MR scanners. CT is fairly limited in the evaluation of cardiac tumors, whereas MR imaging provides far more detail with regard to tissue characterization and the evaluation of tissue planes.

In the case of malignant cardiac tumors, PET is often indicated for staging purposes, owing to the improved sensitivity of PET for metastatic disease in comparison with anatomic imaging alone. PET is also often used for the evaluation of treatment effectiveness and for surveillance.

When both anatomic and metabolic imaging is indicated in the evaluation of a cardiac tumor, PET/MR may be superior to PET/CT. The primary tumor almost certainly would be more clearly demonstrated by MR imaging, and even in the evaluation for nodal and metastatic disease, PET/MR would likely be similar or superior to PET/CT.<sup>20</sup> Although this supposition has not specifically assessed for cardiac malignancies, several studies have reported on the value of PET/MR in comparison with PET/CT for a variety of other tumors, including lung cancer.<sup>21</sup> One notable weakness of PET/MR is in the evaluation of the lungs.

## MYOCARDIAL ISCHEMIA AND INFARCTION

The extent of patients' coronary artery disease (CAD) can be evaluated by cardiac MR imaging, although the modality is not considered first line for this indication. First-pass perfusion with gadolinium can demonstrate perfusion defects at stress and rest, analogous to nuclear perfusion studies.<sup>22</sup> Direct coronary artery imaging is also possible by MR imaging,<sup>23</sup> although coronary CT angiography is currently the noninvasive gold standard owing to its high resolution and fast acquisition times.

Cardiac MR imaging is more commonly used in the evaluation of myocardial infarctions. Late gadolinium enhancement (LGE) is demonstrated in acute and chronic infarctions, with the contrast being retained in the expanded extracellular in necrotic myocardium early and in regions of fibrosis later.

Myocardial perfusion with PET tracers such as N-13 ammonia and Rb-82 is used more commonly than MR imaging to evaluate for CAD (Fig. 2). PET perfusion studies have high sensitivity and specificity for the evaluation of obstructive CAD,<sup>24–26</sup> and the PET data can also be processed to quantify coronary artery blood flow. This assessment is of particular value in patients with balanced ischemia, which can be underappreciated on visual evaluation.<sup>27,28</sup>

Like cardiac MR imaging, infarctions may also be demonstrated by PET. Myocardial infarctions on PET imaging are seen as matched perfusion defects on both rest and stress, although hibernating myocardium can have a similar appearance.

Hybrid PET/MR systems may be particularly well suited for the evaluation of patients with suspected CAD and/or infarctions. Specifically, the strengths of MR imaging and PET each could theoretically complement weaknesses in the other, all with the ease of a single imaging session.<sup>29</sup> In particular, fully integrated systems may allow for simultaneous PET and MR acquisition after a single administration of a myocardial stress agent. Most intriguingly, perhaps, is the ability to evaluate for CAD/infarctions (relying heavily on the PET images) and viable myocardium (relying mostly on the MR images) in one session. Assessing for viability by PET usually requires the administration of a different radiotracer (FDG) than those used for perfusion; MR imaging only requires the administration of gadolinium (see later discussion).

Another potential application for combined PET/MR systems is the differentiation of ischemic and nonischemic cardiomyopathies. At present, PET

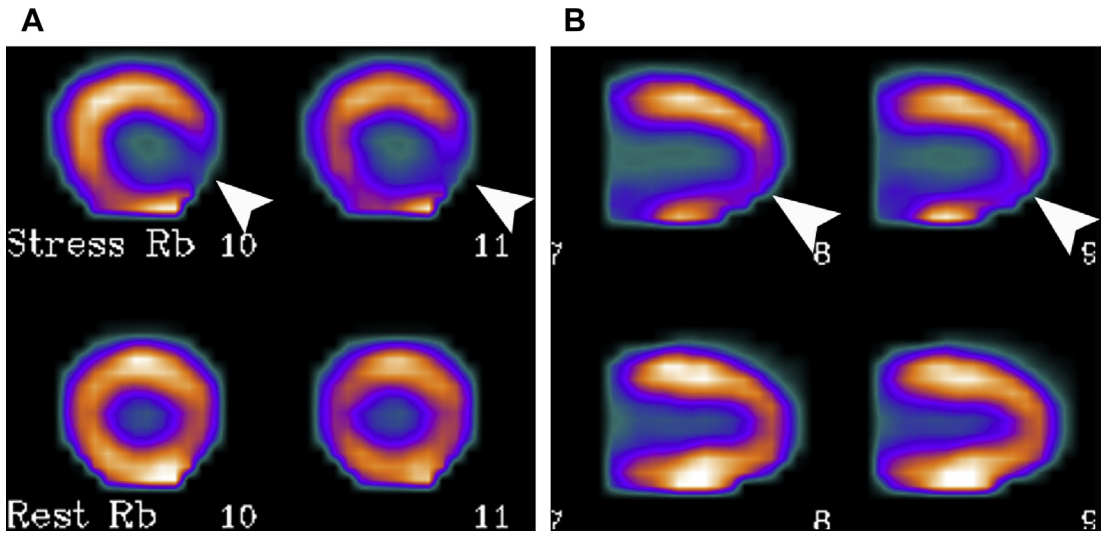


Fig. 2. Reduced myocardial perfusion during stress: Short-axis (A) and vertical long-axis (B) images from an Rb-82 stress (top rows) and rest (bottom rows) myocardial perfusion PET study show an inferolateral wall (white arrowheads) reversible perfusion defect in a 79-year-old man who presented for preoperative clearance before lumbar laminectomy.

and MR both provide imperfect information to differentiate between the two. PET can identify areas of decreased perfusion, areas of viability, and regions at risk, while MR is excellent at assessing myocardial scarring and functional information. The simultaneous acquisition of PET and MR data may allow for a more accurate overall assessment.

### VIABILITY

Cardiac MR imaging suggests viable myocardium when nonenhancing myocardium is seen adjacent to subendocardial infarcts on late gadolinium enhancement sequences. No special patient preparation is needed, and the sequences used are the same that identify the necrotic myocardium and scar.

PET suggests viable myocardium when FDG uptake is demonstrated in regions of fixed, decreased perfusion (Fig. 3). PET is widely considered the gold standard for assessing for viable myocardium that could benefit from revascularization.<sup>30–32</sup> In repetitively stunned or chronic hypoperfused myocardium, anaerobic metabolism is favored, which results in the elevated glucose uptake visualized with FDG. Conversely, scarred myocardium shows absent perfusion and absent FDG uptake (Fig. 4).

Simultaneous PET/MR acquisition has the potential of merging these two powerful techniques into one. The molecular information of FDG PET combined with the structural and functional

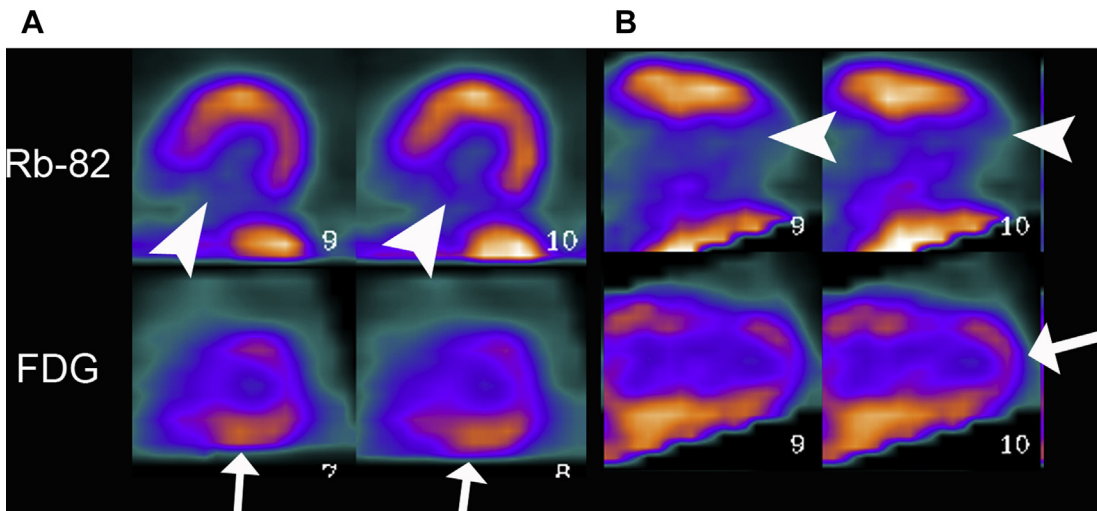
information obtained from MR may add additional diagnostic sensitivity or specificity. In hybrid PET/MR studies in which only perfusion agents are administered for the PET, the MR evaluation could preferentially provide information about possible viability.

### SARCOIDOSIS

Cardiac sarcoidosis, a potentially fatal disease in which noncaseating, nonnecrotic granulomas develop in the myocardium, may be particularly well suited for imaging with hybrid PET/MR systems.<sup>33</sup>

Cardiac MR imaging can reveal the active inflammation phase of sarcoidosis. Focal wall thickening, focal wall motion abnormalities, increased signal intensity on T2-weighted images, and early gadolinium enhancement<sup>34</sup> can all be seen in this phase. Fibrosis, seen in the chronic phase of the disease, is demonstrated by late gadolinium enhancement.<sup>35</sup> Overlap of these 2 phases and, therefore, overlap of these imaging patterns, is possible.

PET also demonstrates abnormalities in the inflammation and fibrotic phases of sarcoidosis. FDG uptake suggests inflammation (Fig. 5),<sup>36</sup> which notably relies on glucose uptake, rather than the mechanisms indirectly imaged by MR imaging (edema, expanded extracellular space, and so forth). Myocardial fibrosis is demonstrated on PET perfusion studies, usually as focal perfusion defects.<sup>37</sup> The PET evaluation of sarcoidosis with



**Fig. 3.** Viable myocardium: Short-axis (A) and vertical long-axis (B) images from resting Rb-82 PET (top rows) and [ $^{18}\text{F}$ ] fluorodeoxyglucose (FDG) PET viability study (bottom rows) in a 56-year-old man with a history of endocarditis and severe mitral valve regurgitation. The patient originally presented with severe cardiogenic shock and was found to have a large fixed perfusion defect at another hospital (not shown). Perfusion images show a large, severe defect involving the distal inferior wall and much of the apex (white arrowheads). These regions demonstrated moderate FDG uptake on the select short-axis images and subtle FDG uptake in the apex on the selected vertical long-axis images (white arrows), compatible with regions of viable myocardium.

FDG requires a patient preparation that suppresses normal use of myocardial glucose. A variety of preparations have been proposed with varying success, including prolonged fasting,<sup>38</sup> high-fat low-carbohydrate diets,<sup>39</sup> and the administration of intravenous nonfractionated heparin.<sup>36,38</sup> In addition, PET suffers from a somewhat lower spatial resolution than MR imaging.

Although a clear gold standard is lacking in making the diagnosis of cardiac sarcoidosis, PET and MR imaging both appear to have imperfect sensitivity and specificity, most notably with PET demonstrating a relatively weaker specificity.<sup>40</sup> Because PET and MR imaging rely on different underlying mechanisms in this disease, the combination of the two could increase the overall diagnostic accuracy.<sup>33,41</sup>

## MYOCARDITIS

Other causes of myocardial inflammation also demonstrate abnormalities on PET and MR imaging. Myocarditis resulting from infection, autoimmune mechanisms, toxin exposure, allergic reactions, or idiopathic causes can result in hyperemia, edema, wall motion abnormalities, necrosis, and fibrosis. These pathophysiologic processes can be visualized by MR imaging. Indeed, diagnostic criteria using MR imaging findings have been published.<sup>42</sup> FDG PET has less

extensively been studied in the evaluation of myocarditis, although increased FDG uptake has been described in this setting. Ozawa and colleagues<sup>43</sup> described overall moderate sensitivity and good specificity in demonstrating the inflammation of myocarditis via FDG PET in a comparison with endomyocardial biopsy. Imaging within 2 weeks of symptom onset demonstrated particularly high sensitivity and specificity. Studies of simultaneous PET/MR imaging for this indication have not been published thus far, although this is a potential area of interest.

## OTHER POTENTIAL APPLICATIONS AND FUTURE DIRECTIONS

PET and MR technology is likely to continue to advance, particularly with large improvements expected in combined systems. New contrast agents and radiotracers also hold the promise of new applications for stand-alone and combined PET/MR systems. Already a multitude of PET tracers are at various stages of development, including tracers that localize to regions of apoptosis, hypoxia, protein synthesis, DNA synthesis, and angiogenesis. Some investigators have even been developing dual-modality agents that contain both a radionuclide and magnetic nanoparticles.<sup>44,45</sup>

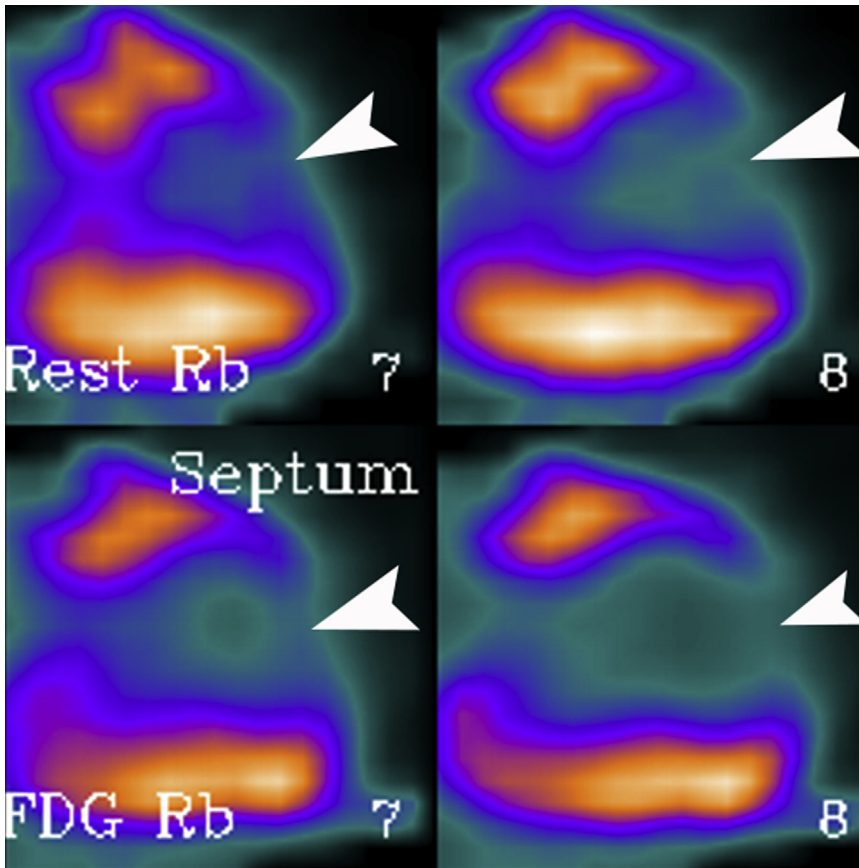


Fig. 4. Myocardial scarring from a myocardial infarction: Vertical long-axis images from an Rb-82 rest (top row) myocardial perfusion PET study show a large anterior wall perfusion defect that extends into the apex (top white arrow heads). The FDG viability PET study (bottom row) shows a matched metabolic defect (bottom white arrow heads), confirming scarring in this 54-year-old man with history of 3-vessel disease and multiple prior coronary artery stents who presented with decreased ejection fraction and a nonreversible perfusion defect on prior myocardial stress test (not shown).

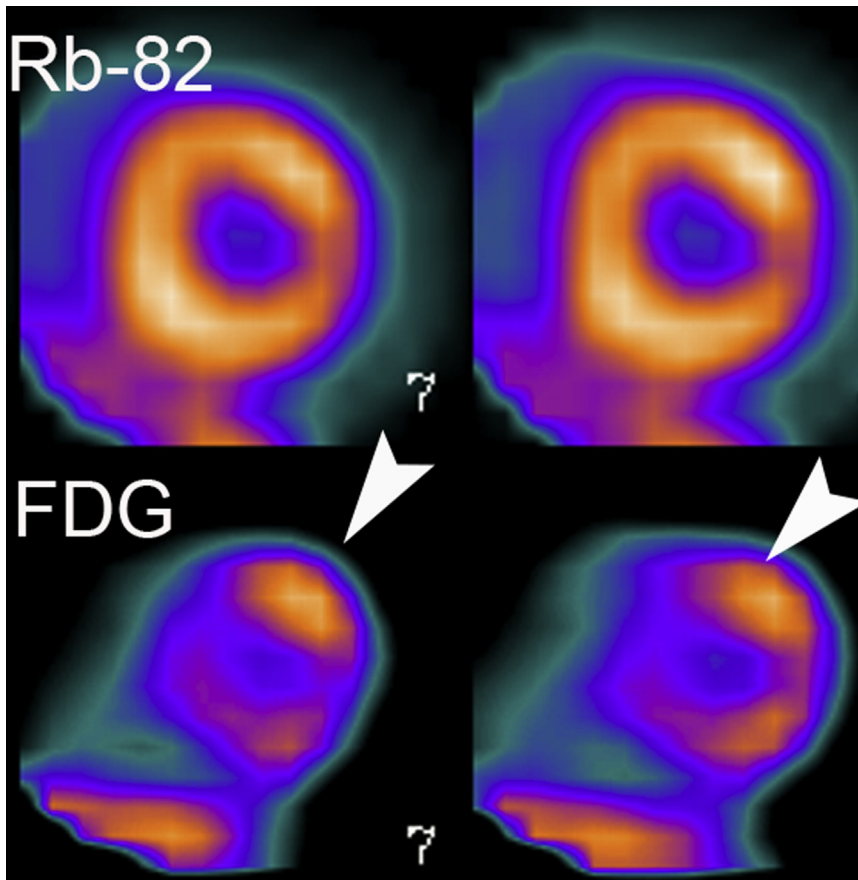
Future research in the following areas may yield new uses for combined PET/MR systems:

- Atherosclerosis: With improved special resolution, MR could potentially evaluate the content of plaques while PET tracers could assess the degree of plaque inflammation,<sup>46</sup> factors that could indicate plaques at risk for rupture.
- Stem cell engraftment: PET/MR may be an optimal imaging system for demonstration of stem cell engraftment.<sup>45,47</sup>
- Sympathetic imaging: Radionuclides such as iodine-124 metaiodobenzylguanidine can be used to assess myocardial sympathetic innervation defects in a variety of conditions, including heart failure.<sup>48</sup>
- Remodeling after myocardial infarction: PET and MR together may optimally identify inflammation in infarcted myocardium, which may reflect increased risk of adverse remodeling.<sup>49,50</sup>

#### LIMITATIONS OF HYBRID PET/MAGNETIC RESONANCE IMAGING

Although there are many enticing features of PET/MR systems, several significant factors could hamper its widespread acceptance into routine clinical care, including:

- Situations in which CT remains superior, including presently the evaluation of the lungs and the coronary arteries.
- Imaging patients with implanted electronic devices or other contraindications to MR imaging. Such devices are common in cardiac patients.
- Imaging patients with severe renal impairment or renal failure, who generally cannot receive gadolinium.
- At present many issues surrounding scheduling, reporting, and billing have yet to be worked out for combined PET/MR studies, which can hinder adoption of this technology in the short term.



**Fig. 5.** Active myocardial sarcoidosis: Short-axis rest Rb-82 (*top row*) and FDG (*bottom row*) PET images from a 35-year-old woman with palpitations and syncope and suspected cardiac sarcoidosis. FDG PET images, which are presented at a slightly lower magnification, show patchy areas of FDG uptake most prominent in the anterolateral wall (*white arrowheads*), suggesting a region of active sarcoidosis. No significant perfusion defect is apparent on this slice (nor on the remaining short-axis slices, not shown), which argues against any significant scarring resulting from chronic cardiac sarcoidosis.

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