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MR/PET Imaging of the Cardiovascular System

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Abstract

Cardiovascular imaging has largely focused on identifying structural, functional, and metabolic changes in the heart. The ability to reliably assess disease activity would have major potential clinical advantages, including the identification of early disease, differentiating active from stable conditions, and monitoring disease progression or response to therapy. Positron emission tomography (PET) imaging now allows such assessments of disease activity to be acquired in the heart, whereas magnetic resonance (MR) scanning provides detailed anatomic imaging and tissue characterization. Hybrid MR/PET scanners therefore combine the strengths of 2 already powerful imaging modalities. Simultaneous acquisition of the 2 scans also provides added benefits, including improved scanning efficiency, motion correction, and partial volume correction. Radiation exposure is lower than with hybrid PET/computed tomography scanning, which might be particularly beneficial in younger patients who may need repeated scans. The present review discusses the expanding clinical literature investigating MR/PET imaging, highlights its advantages and limitations, and explores future potential applications.

Keywords

atherosclerosis; cardiomyopathy; hybrid imaging; MR; PET

The ability to measure disease activity in the cardiovascular system accurately and at a low dose of radiation would be a major clinical advance. Indeed, this approach would allow investigation of the early stages of disease, permit disease activity to be tracked over time or in response to therapy, and allow differentiation of active pathology from quiescent disease

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states. The recent advent of hybrid magnetic resonance (MR) and positron emission tomography (PET) scanners has therefore generated intense interest, potentially combining the strengths of these 2 already powerful imaging modalities. Hybrid MR/PET scanners enable a patient to undergo PET imaging at a lower radiation dose compared with hybrid PET/computed tomography (CT) scanners, which are most commonly available.

Although radiation dose is not necessarily a significant limitation for routine clinical imaging, these reductions are likely to be of particular value in the clinical imaging of younger patients in whom concerns about radiation exposure are greatest and for potentially complex research protocols. Moreover, the simultaneous acquisition of MR and PET data possible on hybrid scanners provides several additional advantages, including accurate co-registration, motion correction, and more efficient, patient-friendly image acquisition.

Technical challenges remain in applying this novel technology to the cardiovascular system; however, solutions are rapidly being developed, and experience is growing worldwide. Indeed, a maturing body of literature has emerged exploring the application of this technology to a wide range of cardiovascular disorders. The present review discusses these recent clinical studies, highlights both the strengths and weaknesses of cardiovascular MR/PET imaging, and explores some of its future applications.

HYBRID PET/CT IMAGING

PET is a highly sensitive imaging technology that measures the activity of specific disease processes as they are occurring in the body. Potentially, any pathological process may be studied dependent on the availability of a targeted radiotracer. After injection into the body, these radiotracers accumulate in areas where the disease process is active, releasing radiation that can be detected by the PET scanner. However, PET imaging is limited by the anatomic information that it provides and thus needs to be combined with a second anatomic imaging modality: CT or MR. These allow the PET data to be localized to specific structures within the body and also permit correction for PET signal attenuation by different tissues in the body (attenuation correction). To date, PET has largely been performed in conjunction with CT scanning, or in standalone PET scanners that use a radioactive source to perform a transmission scan to measure attenuation. Although the radiation dose associated with the transmission scan is negligible, the transmission scan does not provide anatomic reference data and takes many times longer than CT imaging. Moreover, the numbers of standalone PET systems are declining, being replaced by hybrid PET/CT systems. For this reason, the present review focused on comparing hybrid MR/PET imaging with hybrid PET/CT imaging.

Hybrid PET/CT imaging is widely used to study the heart and large arteries. Currently, the principal clinical applications are myocardial perfusion and viability assessments in patients with ischemic heart disease (1). PET perfusion offers several key advantages compared with single-photon emission computed tomography (SPECT), including the ability to quantify perfusion and the ability to detect balanced ischemia and microvascular disease. ^{11}C-labeled fatty acids can be used to assess cardiac metabolism (2), whereas ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is used to investigate myocardial viability. ^{18}F-FDG is a glucose analogue, the

uptake of which reflects cellular glucose uptake and phosphorylation. Given that glucose is a major energy substrate of the myocardium, ^{18}F-FDG uptake can identify areas of viable myocardium, including areas of hibernation with impaired systolic function, and can be used to predict recovery of function after revascularization (3).

An alternative use of ^{18}F-FDG-PET imaging is in the assessment of cardiovascular inflammation. This approach relies on a different mechanism, related to the high uptake of glucose by macrophages and other inflammatory cells. In the heart, high-fat-no-carbohydrate dietary preparation can help switch myocardial metabolism away from glucose to free fatty acids, suppressing physiological ^{18}F-FDG uptake by myocytes and allowing regions of inflammation to be observed. This method has been used to investigate the inflammation associated with myocardial sarcoidosis (4–6), valve endocarditis (7), and cardiac device infection. Although these uses are supported by recent clinical guidelines (8), myocardial suppression of physiological glucose utilization is unsuccessful in approximately one-quarter of patients, leading to the potential for false-positive myocardial ^{18}F-FDG uptake (9).

Coronary ^{18}F-FDG-PET/CT imaging is also limited by myocardial ^{18}F-FDG uptake (9,10); however, this scenario is not a problem for larger arteries remote from the heart. Indeed, carotid and aortic ^{18}F-FDG-PET/CT imaging correlates well with macrophage burden and is used to investigate inflammation related to atherosclerosis and vasculitis (11,12). Because the scan-rescan reproducibility is also very good, demonstration of change in the ^{18}F-FDG signal requires only modest group sizes (11). As a consequence, vascular ^{18}F-FDG-PET/CT scanning is increasingly being used in clinical trials to assess the anti-inflammatory effects of novel atherosclerosis treatments, demonstrating close agreement with the results of larger clinical outcome studies examining clinical outcomes (13).

NOVEL IMAGING TRACERS

Multiple new PET radiotracers are in development and increasingly being used to investigate different aspects of cardiovascular disease in the research setting (Table 1). Most notably, ^{18}F-fluoride-PET/CT imaging has been used to study microcalcification in coronary and carotid atheroma (9,10,14) and as a marker of valve disease activity in patients with aortic stenosis (15,16). Large prospective studies are underway assessing whether ^{18}F-fluoride can improve risk prediction and assess response to therapy in these conditions. Novel MR imaging tracers are also being developed, such as ultra-small particles of iron oxide, dual-modality probes, and other nanoparticles, which could be used to image multiple disease processes together with PET imaging.

MR/PET IMAGING

As with CT imaging, MR imaging provides accurate anatomic detail but also advanced soft tissue contrast, allowing improved discrimination of lesions and pathological changes. MR methods are therefore more naturally suited to imaging many different structures in the cardiovascular system than CT scanning, including the myocardium and carotid arteries. These factors have led many researchers to explore the potential benefits of the newly available hybrid MR/PET imaging technology. However, combining MR and PET into a

single scanner has proved a major technological challenge, primarily due to difficulties in developing PET detectors that will operate effectively within a strong magnetic field (standard PET photo-multiplier tubes do not). Early MR/PET systems involved separate PET and MR scanners with a movable patient table (Ingenuity TF PET/MR, Philips Healthcare, Best, the Netherlands).

However, a major breakthrough came with the development of avalanche photodiode and silicon photomultiplier detectors that were capable of working within the MR scanner (17,18). These paved the way for the development of truly hybrid systems that housed the MR and PET scanners within the same gantry (Biograph mMR, Siemens Healthcare, Erlangen, Germany; Signa PET/MR, GE Systems, Waukesha, Wisconsin). Hybrid MR/PET scanners now offer simultaneous, spatially co-registered imaging, precisely combining the molecular specificity of PET imaging with the anatomy, tissue characterization, and functional information provided by MR imaging. This new generation of MR/PET scanners potentially provide some advantages compared with PET/CT options and versus performing PET/CT and MR imaging individually. Despite the current drawbacks of cost and complexity (Table 2), a single MR/PET scan maintains the advantages of the 2 individual imaging approaches while providing additional potential advantages, discussed in the following text (Central Illustration).

REDUCED RADIATION EXPOSURE.

Levels of radiation exposure in current clinical PET/CT protocols do not pose a significant health risk to general patient groups. Nevertheless, reduced radiation exposure is a key goal in cardiovascular imaging according to the ALARA (as low as reasonably achievable) principle. This approach is particularly true in younger patients, who are most likely to undergo repeated imaging and are most susceptible to the risks of radiation. In the clinical arena, MR/PET imaging is therefore most likely to prove useful in this patient group.

In the research setting, advanced cardiovascular PET/CT protocols increasingly use detailed contrast-enhanced CT angiograms and CT calcium scoring in addition to attenuation correction scans (9,19). The radiation doses from CT in these protocols are therefore high. Moreover, with the recent development of multiple novel PET tracers, there is interest in measuring the activity of multiple processes. This use of more than 1 PET tracer would result in further increases in PET-related radiation. The potential advantages of lower radiation MR/PET imaging are therefore being considered. There is particular interest in longitudinal studies involving multiple complex MR/PET scans to investigate the activity of chronic disease processes over time (e.g., atherosclerosis, valve disease) or before and after an experimental intervention (e.g., administration of a novel therapy). Alternatively, multiple cardiovascular scans using different radiotracers could be performed, allowing the activity of several different disease processes to be investigated. As noted earlier, these MR/PET research protocols would hold greatest value in the imaging of younger patients and the earlier stages of disease.

MOTION AND PARTIAL VOLUME CORRECTION.

The combined effect of both cardiac contraction and respiratory displacement leads to a complex pattern of motion, causing artifact and blurring in the cardiac PET data. Motion correction is therefore an important goal for researchers working in the field and potentially a major strength of hybrid MR/PET compared with PET/CT systems. Motion compensation typically relies on using electrocardiogram gating to accept only PET data acquired during diastole. Although this technique has improved visualization of coronary and valvular PET activity (9,19), it does not account for respiratory variation and discards the majority of PET data acquired. More efficient and sophisticated approaches are, however, feasible. Although cardiac motion can be estimated using the PET data itself (20), an alternative approach is to use anatomic MR imaging to track the motion of the heart directly. The resulting motion information can then be applied to the PET data, correcting for motion artifact. Respiratory motion correction with MR/PET imaging has been successfully applied to liver and lung imaging (21,22). Although cardiac motion is more complex, the basic feasibility has been demonstrated in phantoms and preclinical and clinical studies (23–25), with further research ongoing (26,27).

Partial volume errors arise when tracer uptake bleeds into neighboring voxels causing blurring, inaccuracies in PET quantification, and impaired diagnostic evaluation. Correction of partial volume errors uses sophisticated techniques that incorporate high-resolution anatomic information into the PET reconstruction (28). These may be further improved with the superior soft tissue discrimination provided by hybrid MR/PET imaging. In addition, simultaneous acquisition will avoid the errors associated with the retrospective co-registration of 2 independent scans, leading to further improvements in partial volume errors and motion correction.

SUPERIOR SOFT TISSUE CONTRAST.

MR scanning provides improved soft tissue characterization compared with CT scanning, particularly when imaging the myocardium and atherosclerotic plaque. The ability to easily and accurately co-register this information with disease activity is a major potential advantage of hybrid MR/PET imaging. Cardiac MR cine imaging provides high contrast between the blood pool and myocardium and excellent temporal resolution, allowing accurate evaluation of cardiac volumes, mass, wall motion, and ejection fraction. In the myocardium, the late gadolinium enhancement (LGE) approach is used clinically to identify areas of myocardial injury and cardiac infiltration in a range of cardiac conditions. More sophisticated techniques are emerging, including T1-mapping for diffuse myocardial fibrosis; T2-mapping for myocardial edema; and T2*-mapping for myocardial iron deposition (29).

MR scanning offers powerful assessment of atherosclerotic plaque composition, particularly in the carotid arteries (30,31). High in-plane resolution imaging with multicontrast T1, T2, and proton-density weighting has become the gold standard approach to identifying positive remodeling and lipid-rich necrotic core. Prospective studies have confirmed that T1-weighted MR imaging of acute plaque hemorrhage or intraluminal thrombus formation accurately identifies culprit and high-risk plaque in the carotids and coronary arteries, as

well as patients with an increased risk of future cardiovascular events (31–33). Finally, administration of gadolinium contrast allows identification of thin or ruptured fibrous caps (34) and plaque angiogenesis (35), whereas ultra-small paramagnetic iron oxide nanoparticles can be used to assess plaque macrophage infiltration (36).

MULTIPARAMETRIC MULTIORGAN ASSESSMENTS.

The absence of radiation allows for complex MR protocols to be performed, collecting a wide spectrum of information about the cardiovascular system and beyond. This collection might include anatomic assessments of multiple vascular beds, including the coronary arteries, carotid arteries, and aorta, but also radiation-free investigation of cardiac function and flow hemodynamic parameters, as well as the advanced soft tissue characterization described earlier. In addition, non-cardiac structures can be imaged to investigate the systemic influences and consequences of cardiovascular disease. Potential areas of study include the association of emotional stress with cardiovascular inflammation (37), vascular disease with neurocognitive disorders (38), and vascular calcification with skeletal bone metabolism (39).

RECENT APPLICATIONS OF CARDIOVASCULAR MR/PET IMAGING

This section describes the recent exploratory and feasibility studies that have investigated the potential clinical utility of MR/PET imaging across a range of cardiovascular disorders. These studies have generally involved relatively small numbers of patients, and confirmation in larger multicenter studies is therefore required.

AGREEMENT BETWEEN MR/PET AND PET/CT IMAGING.

Two recent studies including a total of 40 patients (40,41) compared quantification of carotid ^{18}F-FDG activity using MR/PET versus PET/CT imaging. Standard uptake values were well correlated but indicated a small but significant underestimation by MR/PET scans, likely due to differences in attenuation correction. Another study investigated myocardial ^{18}F-FDG uptake values using MR/PET and PET/CT imaging (42). Twenty-seven patients underwent the 2 scans within 1 h of each other after a single injection. Importantly, only minor differences in the normalized standard uptake values were observed, indicating that myocardial PET tracer quantification on the 2 scans is broadly similar. Further research is required to assess the impact of different methods for MR attenuation correction and whether uptake values are similar in different disease states.

MYOCARDIAL DISEASE.

Ischemic heart disease.—^{18}F-FDG-PET and MR scanners are widely used to assess myocardial viability in patients with ischemic heart disease. Both techniques have shown excellent diagnostic accuracy and provide important prognostic information. In a recent study, 21 patients post-myocardial infarction were imaged with hybrid MR/PET scanners (43) to correlate cardiac function, area-at-risk, glucose metabolism, and infarct size. The investigators demonstrated close agreement between the area-at-risk, delineated by ^{l8}F-FDG-PET, and MR T2-mapping, both of which were larger than that observed with LGE. LGE transmurality and ^{l8}F-FDG uptake performed equally well in predicting myocardial

functional recovery. In another study of 28 post-myocardial infarction patients (44), moderate agreement between MR and PET assessments of viability was shown (kappa = 0.65), with both modalities again accurately predicting recovery in regional wall motion after 6 months. Although these studies have demonstrated the feasibility of hybrid MR/PET imaging in patients after myocardial infarction, the incremental value of MR/PET versus existing techniques remains to be demonstrated. The same is true of myocardial perfusion imaging. Further studies are required in these areas, particularly in younger patients.

Cardiac sarcoidosis.—One of the most exciting potential clinical applications of MR/PET imaging is in the assessment of cardiac sarcoidosis. MR imaging informs about myocardial structure, function, and the pattern of injury on LGE, whereas ^{18}F-FDG-PET informs about myocardial and extra-cardiac inflammation. Moreover, the ability to easily and accurately fuse MR/LGE and FDG/PET images facilitates cross-referencing of the image findings, aiding in the interpretation of both scans. Finally, both MR and PET scans are recommended in current clinical guidelines for the investigation of suspected cardiac sarcoidosis (45). When both assessments are required, their completion within a single scan streamlines the patient pathway and improves cost-effectiveness.

Several groups have now investigated the feasibility of MR/PET imaging in cardiac sarcoidosis. Initial studies investigated the benefits of co-registering scans acquired on separate MR and PET scanners (46,47), demonstrating improved scan interpretation compared with side-by-side evaluation of the independent scans.

Hybrid ^{18}F-FDG-MR/PET imaging in patients with suspected cardiac sarcoidosis was first described in case report format, providing early illustration of the advantages of simultaneous scanning (48,49). First, accurate co-registration was achieved rapidly in 3 orthogonal planes between the PET data and contrast-enhanced 3-dimensional MR angiograms of the heart. Subsequently, LGE images were fused with the PET data, demonstrating accurate co-localization of increased ^{18}F-FDG activity with areas of myocardial injury observed on LGE. In a larger cohort of 25 patients with suspected active cardiac sarcoidosis, patients were categorized into 4 groups (50). $MR^{+}PET^{+}$ patients demonstrated increased ^{18}F-FDG uptake co-localizing with regions of LGE and were considered to have imaging evidence of active cardiac sarcoidosis (Figure 1). $MR^{+}PET^{-}$ patients had characteristic LGE appearances but no increase in ^{18}F-FDG activity, suggesting chronic scarring secondary to “burnt-out” sarcoidosis, whereas $MR^{-}PET^{-}$ patients had no evidence of cardiac sarcoidosis involvement. The most challenging group to interpret were the 8 $MR^{-}PET^{+}$ patients, 6 of whom had diffuse uptake throughout the myocardium. This finding is not consistent with the patchy nature of cardiac sarcoidosis involvement, and the myocardial uptake also showed a dynamic PET profile different from that of patients in the $MR^{+}PET^{+}$ group. These patients were therefore believed to have false-positive ^{18}F-FDG uptake related to failed myocardial suppression. However, 2 of the $MR^{-}PET^{+}$ patients had focal increases in ^{18}F-FDG activity localizing to the inferolateral wall in the absence of any LGE changes. Although such patterns could relate to myocardial inflammation visible on PET but not MR imaging, in these particular subjects, the magnitude and dynamic profile of the ^{18}F-FDG uptake was the same as that observed in patients with physiological false-positive uptake.

Considerable caution is therefore required when interpreting the results of myocardial ^{18}F-FDG-PET imaging alone. However, MR/PET imaging seems to be helpful in this regard, allowing cross-referencing with MR-LGE images and the dynamic profile of the uptake to be assessed during the longer bed times. Additional studies are now required to investigate these initial findings and to assess whether hybrid MR/PET scanners improve the diagnostic accuracy and prediction of adverse outcomes compared with the current standard of care. Importantly, in both of the aforementioned studies, ^{l8}F-FDG-PET scanning appeared to outperform T2-mapping in the identification of active myocardial disease, supporting the guidelines and the requirement for an additional PET scan.

Myocarditis.—Patients with myocarditis commonly present with troponin-positive chest pain but a normal coronary angiogram. MR scanning is already widely used to confirm the diagnosis and rule out myocardial infarction based on the characteristic pattern of mid-wall LGE. In certain cases, addition of ^{l8}F-FDG-PET scanning might prove complementary, indicating whether the underlying disease process is active (Figure 2) (48). In a study of 65 patients with suspected myocarditis, hybrid ^{18}F-FDG-MR/PET scanning was performed, including LGE and T2-weighted imaging (51). Eight patients had failed myocardial suppression despite dietary restrictions, and 2 were unable to complete imaging due to claustrophobia. In the remainder, agreement between ^{l8}F-FDG-PET and cardiac MR was good (kappa = 0.73) with the closest association observed between PET and T2-mapping values. Further studies in this condition are required.

Cardiac amyloidosis.—MR scanning is a well-established tool in the diagnosis of cardiac amyloidosis. However, MR scanning is unable to differentiate between the 2 predominant forms of amyloid: acquired monoclonal immunoglobulin light-chain and transthyretin related (TTR). This clinical distinction is becoming increasingly important given their different prognoses and emerging treatments. Recently, SPECT imaging has been used to address this problem, based on the increased binding of bisphosphonate bone tracers to TTR amyloid (52,53). Trivieri et al. (54) recently showed that, similar to SPECT, patients with TTR amyloid exhibited increased myocardial activity of the PET bone tracer ^{l8}F-fluoride than patients with acquired monoclonal immunoglobulin light-chain amyloid and matched control patients. Moreover, increased PET activity was observed to co-localize with the pattern of injury observed on LGE (Figure 3). An important advantage of using PET scanning compared with SPECT is that it allows quantification of uptake, with a tissue-to-background uptake value of 0.85 appearing to provide clear distinction between groups. Similar results were also recently observed in a small ^{l8}F-fluoride PET/CT study (55) and although confirmation is required in larger patient cohorts, cardiac amyloidosis remains an exciting area in which MR/PET imaging might rapidly find a clinical role.

ATHEROSCLEROTIC PLAQUE.

MR/PET imaging is particularly well suited to atherosclerotic plaque imaging in the large arteries (carotid, aorta, and femorals) (56–59). In a study of 16 patients, multi-spectral MR and CT imaging were used to classify carotid and femoral atherosclerotic plaques as lipid-necrotic, collagen-rich, or calcified. Of these, the lipid-necrotic plaques demonstrated the highest ^{18}F-FDG uptake (58). In another study of 25 patients undergoing carotid

endarterectomy, ^{18}F-FDG-PET scanning correctly identified all the lesions with a large necrotic core on histology, whereas T1-weighted MR scanning demonstrated good accuracy in the detection of large intra-plaque hemorrhage (specificity 100%; sensitivity 70%) (59). Several studies have compared ^{l8}F-FDG-PET/CT imaging with MR assessments of vascular inflammation, including dynamic contrast-enhanced MR imaging (60,61) and ultra-small paramagnetic iron oxide nanoparticle imaging in both carotid atheroma (62) and abdominal aortic aneurysms (63).

Coronary artery imaging using MR/PET scanners is challenging due to both the small caliber of these vessels and their complex motion. Although MR angiography techniques are able to reliably image the proximal coronary arteries, CT scans remain the preferred modality (29); thus, coronary PET imaging has almost exclusively been performed using PET/CT scanning. Nevertheless, research interest in coronary MR/PET imaging persists because of the benefits related to motion correction and radiation exposure and because MR angiography achieves sufficient spatial resolution to allow PET activity to be mapped to the coronary vessels. Recently, in a study of 23 patients, Robson et al. (64) reported the feasibility of coronary MR/PET imaging using ^{18}F-fluoride. This study highlighted extensive PET artifact at the heart-lung and lung-diaphragm borders when using standard breath-held, attenuation correction maps that frequently rendered PET activity in the coronary arteries uninterpretable. However, this artifact was corrected using a free-breathing, motion-insensitive MR attenuation correction map (3-dimensional golden-angle radial, spoiled-gradient-echo), enabling identification of ^{18}F-fluoride hotspots within the coronary arteries in 7 patients (Figure 4). Increasing the number of iterations of the PET reconstruction further improved image quality.

CARDIAC MASSES.

Cardiac masses were one of the first cardiovascular conditions to be investigated with MR/PET scanners. MR imaging provides anatomic and functional information, as well as detailed soft tissue characterization. In some cases, MR imaging can accurately diagnose specific masses with no need for further investigation (e.g., cardiac fibroma, ventricular thrombus); however, findings are frequently nonspecific, and it often remains unclear even whether a mass is benign or malignant. ^{l8}F-FDG-PET imaging has been widely used in oncological practice to make this distinction, suggesting that MR/PET imaging might prove of incremental value. Yaddanapudi et al. (65) fused separately acquired MR and PET data and found that the complementary information from the 2 scans aided in the diagnosis of 6 patients with cardiac masses, in particular distinguishing benign from malignant lesions. In a study of 20 patients who underwent hybrid MR/PET scanning, ^{l8}F-FDG-PET scanning had a sensitivity of 100% and specificity of 92% for the differentiation of malignant versus benign cardiac masses (66). MR scans, including functional cine and T2-weighted imaging, revealed very similar results, but when the data from the 2 modalities were combined, 100% sensitivity and specificity were achieved.

FUTURE POTENTIAL APPLICATIONS

There are a number of other cardiovascular applications in which hybrid MR/PET technology is anticipated to be advantageous, although these applications have yet to be investigated. Multiple different cardiomyopathies are under investigation with existing radiotracers (67), while the development of new PET and MR tracers, targeting different pathological processes, seem set to rapidly expand our ability to measure disease activity in the myocardium (Table 1).

Both MR and PET scans are increasingly being applied in research studies to patients with heart valve disease. In aortic stenosis, MR imaging can provide assessments of both the valve (peak aortic valve jet velocity and planimetered aortic valve area) and the remodeling response of the left ventricle (hypertrophy, function, and myocardial fibrosis) (68,69). Cardiac MR imaging is also used to quantify aortic and mitral regurgitation, particularly eccentric jets and paraprosthetic lesions, which are difficult to assess with echocardiography. PET imaging has been explored in valvular heart disease using 2 tracers: ^{18}F-fluoride PET/CT scanning as a marker of calcification activity (15,70) and ^{18}F-FDG to investigate patients with endocarditis. The feasibility of MR/PET imaging in aortic stenosis has recently been shown (71).

Similarly, there is research interest in using MR/PET imaging in patients with congenital heart disease, in whom cardiac MR is considered the gold standard anatomic imaging technique. PET might be useful in detecting calcific degeneration and endocarditis of the implanted valves and conduits.

The wide spectrum of available MR measurements will also spur more novel MR/PET applications. For example, Gullberg et al. (72) used MR/PET imaging to investigate cardiac efficiency in heart failure by relating total mechanical work (measured with functional MR scans) to chemical energy consumption (measured by using ^{11}C-acetate PET scans). Similarly, dynamic PET and MR spectroscopy could be used to image cellular metabolism (73) or metabolite synthesis. Moreover, advanced hyperpolarized ^{13}C MR imaging and spectroscopy could be considered for imaging metabolites in the heart (74). The current and future cardiovascular applications of MR/PET scanning are summarized in Table 3.

Future avenues for development in MR/PET imaging are 2-fold. First, technical developments are underway to solve remaining problems (see the following discussion) and to investigate the leverage of the advantages of motion correction and partial volume correction. Second, clinical studies are needed to explore the potential applications discussed here and to evaluate their clinical role together with existing MR and PET/CT protocols.

DISADVANTAGES OF MR/PET IMAGING AND BARRIERS TO FUTURE ADOPTION

Despite the numerous potential advantages of MR/PET imaging, substantial obstacles remain to its widespread adoption in both the clinical and research arenas (Table 2).

TECHNICAL OBSTACLES.

The primary technical challenge for MR/PET imaging is attenuation correction, which is the process by which the collected PET data are corrected for attenuation by the tissues of the body and the components of the MR scanner. The MR receiver coils sit between the PET detectors and the body, potentially attenuating the PET signal and introducing artifact. However, research has shown that the impact of this effect on cardiovascular uptake is in practice minimal because of the low absorption cross-section of the coils and their distance from cardiovascular tissue (75). In contrast, accurate attenuation correction for surrounding tissues in the body is essential. CT scanning offers accurate attenuation correction because the Hounsfield unit of X-ray attenuation is readily transformed into the equivalent linear attenuation coefficient for PET photons.

The approach for MR/PET imaging is more complex. An MR image must first be segmented into different tissue classes, which are then assigned an attenuation coefficient based on their known CT characteristics. Typically, 4 tissue classes (air, lung, fat, and soft tissue) are assigned on images acquired using multi-echo gradient-echo MR imaging (76). Bone is not included in these attenuation correction maps because it is effectively invisible on conventional MR imaging. This issue is a potential problem when examining tissue in close proximity to bony structures given their strong attenuation of PET photons. The development of advanced ultra-short and zero-echo time MR techniques to image bone may solve this significant problem (77).

Estimation of attenuation correction at the edge of the field of view is another issue because the magnetic field becomes inhomogeneous in these areas. Image fidelity and attenuation estimates of the arms are therefore degraded, particularly in obese patients. Advanced PET reconstruction algorithms that simultaneously estimate attenuation and activity based on the nonattenuated PET signal might solve this problem (78) as might MR-based techniques (79).

Metallic implants, including coronary stents and prosthetic valves, cause more severe artifact in MR imaging than in CT imaging. These affect attenuation correction as well as anatomic and functional imaging. Although MR sequences are available to mitigate some of these effects (80), this factor may prove a major limitation for MR/PET imaging in patients with advanced cardiovascular disease and previous percutaneous or surgical intervention.

OPERATIONAL OBSTACLES.

MR/PET imaging is associated with several operational obstacles, including the small bore size of MR/PET scanners, which might increase the likelihood of patient claustrophobia. Moreover, MR/PET systems are currently not widely available, and there is a lack of cardiologists, radiologists, and technologists with training in both modalities. There are also important financial considerations: MR/PET scanners are both expensive to purchase and run while uncertainty persists about the level of reimbursement that insurance companies will offer for hybrid MR/PET examinations. These systems are therefore unlikely to generate clinical revenue from cardiac imaging in the short term. However, MR/PET scanners can also be used to image other organ systems, demonstrating particular promise in the investigation of neurodegenerative disorders (81) and common cancers such as head,

neck, and prostate cancer (82,83). This potentially broad application has encouraged an expanding number of health care providers to invest in this cutting edge, yet expensive, imaging technology.

CONCLUSIONS

MR/PET scanning is an exciting novel imaging modality that can assess disease activity together with assessments of cardiac anatomy, function, and tissue composition during a single scan. The lower associated radiation doses may be particularly important for the clinical imaging of younger patients. In the research arena, beyond the ability to easily combine and co-register already established MR and PET imaging techniques into a single scan, many researchers are seeking novel complex applications that may further advance the state-of-the-art. Although technological and operational obstacles persist, these are rapidly being overcome, positioning MR/PET scans as a useful new imaging modality for the investigation of cardiovascular disease. Further clinical trials are now required to explore the potential of this technique.

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ABBREVIATIONS AND ACRONYMS

CT	computed tomography
FDG	fluorodeoxyglucose
LGE	late gadolinium enhancement
MR	magnetic resonance
PET	positron emission tomography
SPECT	single-photon emission computed tomography
TTR	transthyretin-related

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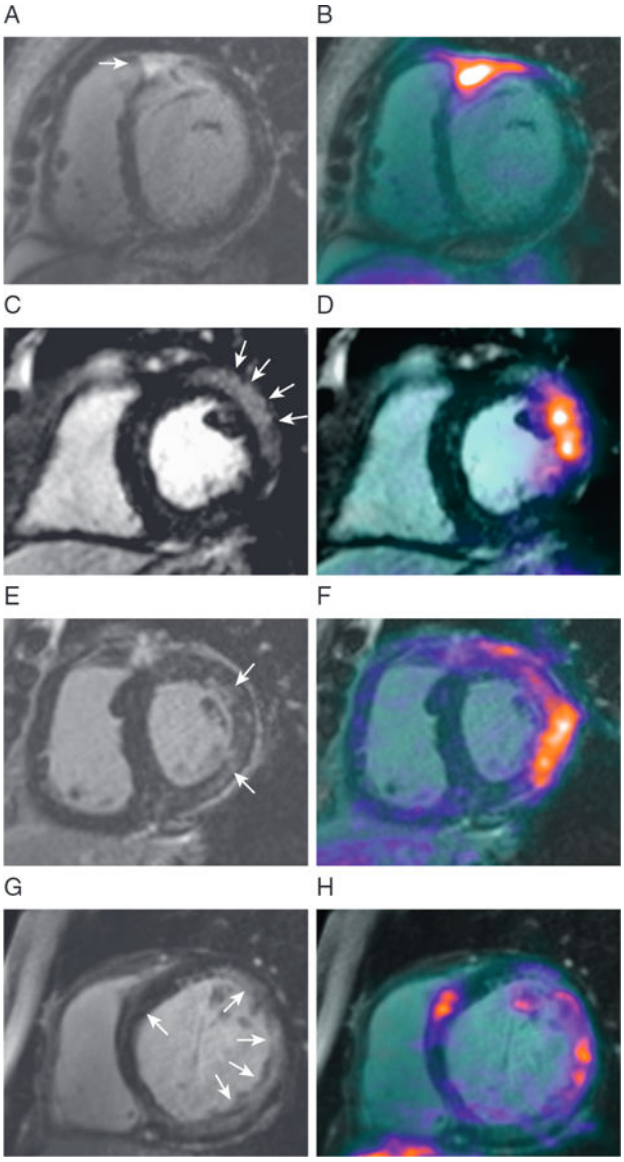


FIGURE 1. MR/PET Imaging in Cardiac Sarcoidosis

Magnetic resonance (MR) and positron emission tomography (PET) images from 4 patients with active cardiac sarcoidosis in whom characteristic patterns of myocardial late gadolinium enhancement **(left column)** co-localize with increased ^{18}F-fluorodeoxyglucose uptake (fused images, **right column**) (50).

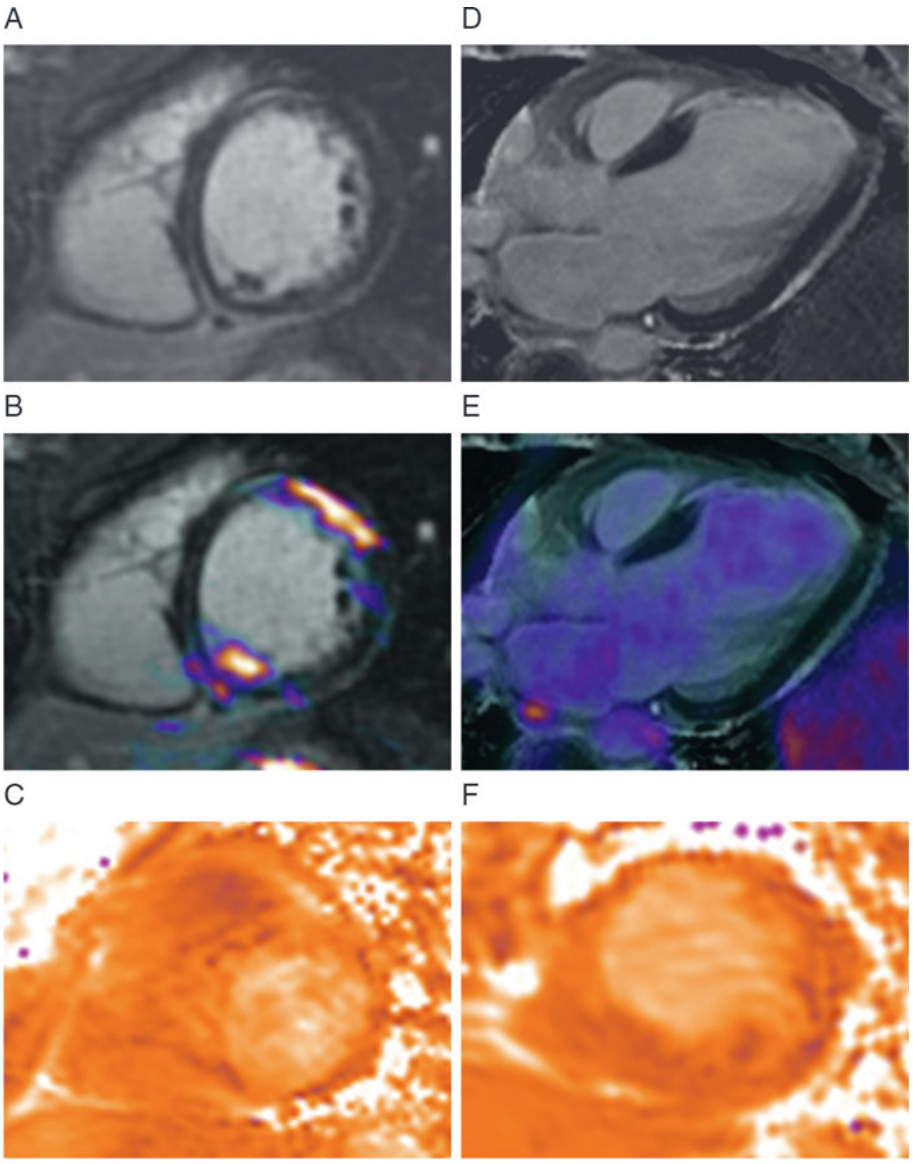


FIGURE 2. MR/PET Imaging in Patients With Acute Chest Pain

MR/PET imaging of a 25-year-old woman with pericarditic chest pain. **(A)** The late gadolinium enhancement (LGE) images demonstrate linear mid-wall LGE consistent with myocarditis. **(B)** Increased ^{18}F-fluorodeoxyglucose (^{18}F-FDG)-PET uptake co-localized with LGE on fusion image indicating active disease, whereas **(C)** T2-mapping could not clearly differentiate regions of myocardial inflammation. **(D)** MR/PET image of a 50-year-old woman presenting with heart failure demonstrating transmural LGE in the anterior wall. **(E)** No increase in ^{18}F-FDG uptake was observed in this region, consistent with an old, previously unrecognized myocardial infarction. **(F)** Again, T2-mapping was inconclusive (48). Abbreviations as in Figure 1.

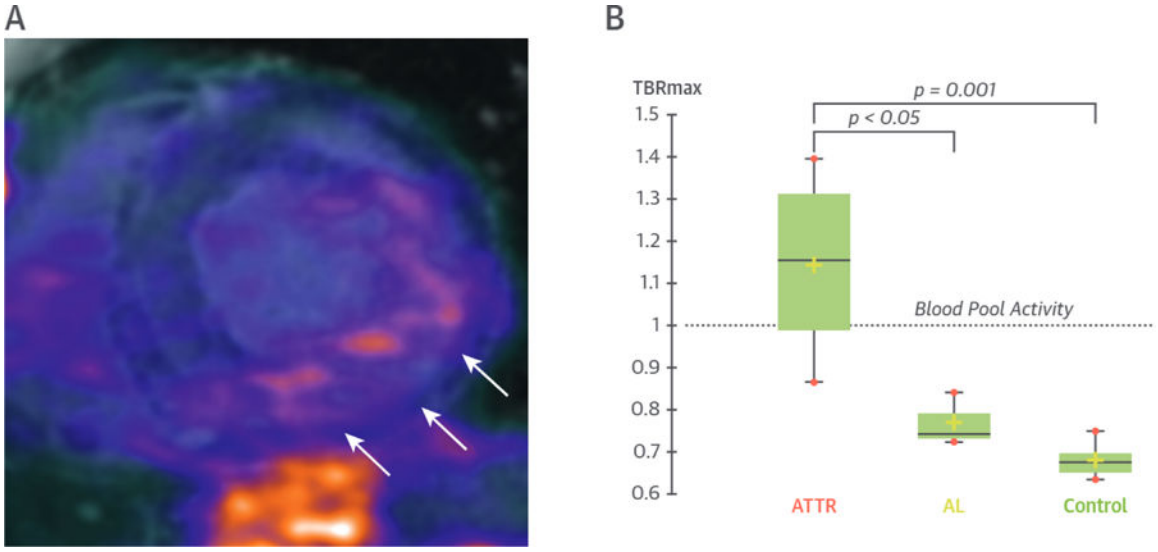


FIGURE 3. MR/PET Imaging in Cardiac Amyloidosis

Patient with transthyretin-related amyloidosis (ATTR). **(A)** Short-axis fused MR/PET image demonstrating increased myocardial ^{18}F-sodium fluoride uptake co-localizing to areas of LGE **(white arrows)** in the inferolateral wall. **(B)** PET uptake in patients with ATTR was 48% higher than in subjects with acquired monoclonal immunoglobulin light-chain (AL) amyloid and 68% higher than in control subjects (54). TBRmax = maximum tissue-to-background; other abbreviations as in Figures 1 and 2.

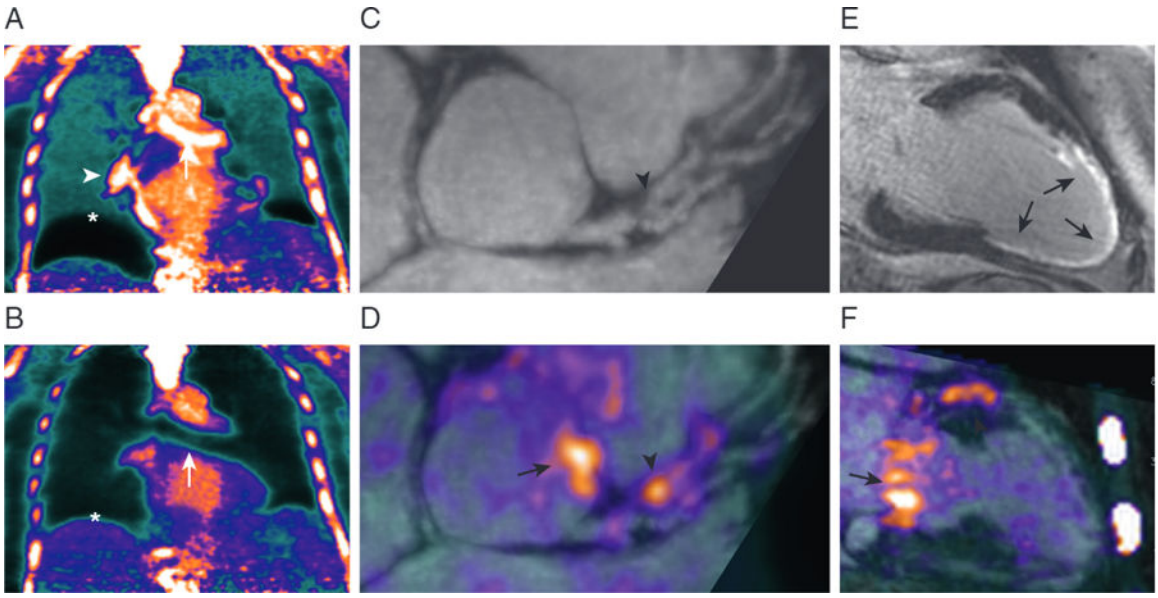
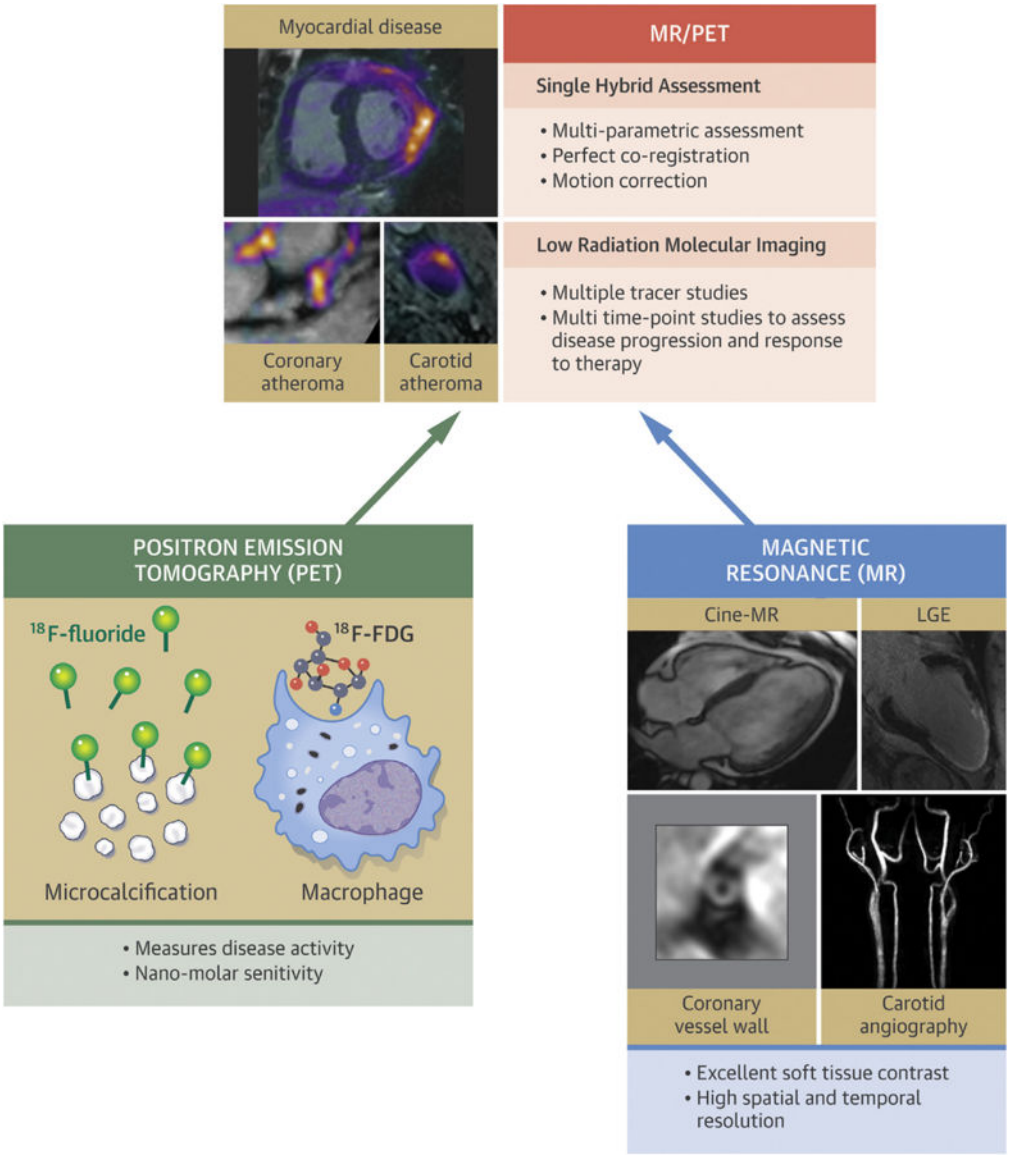


FIGURE 4. MR/PET Imaging of Coronary Atherosclerosis

Patient with breathlessness underwent ^{18}F-sodium fluoride-MR/PET imaging. **(A)** Standard breath-held attenuation correction leads to artifacts at the diaphragm **(*)**, heart-lung boundary **(white arrowhead)**, and bronchus **(white arrow)**. **(B)** These artifacts were corrected with a free-breathing MR sequence for attenuation correction, **(C,D,F)** allowing an area of increased ^{18}F-fluoride uptake to be visualized overlying an obstructive plaque **(black arrowhead)** in the left anterior descending artery. Additional uptake was observed in the aortic wall and mitral valve annulus **(black arrows)**. **(E)** Transmural LGE was observed in the perfusion territory of this lesion, suggesting recent plaque rupture and myocardial infarction (64). Abbreviations as in Figures 1 and 2.



CENTRAL ILLUSTRATION. Hybrid MR/PET Imaging: The Whole Is Greater Than the Sum of its Parts

Not only can the strengths of each modality shown at the base of the pyramid be achieved in a single scan, but hybrid imaging provides additional advantages, including perfect co-registration, improved motion correction, and low-radiation imaging compared with positron emission tomography (PET)/computed tomography (CT) imaging. This combination has the potential to improve the characterization of cardiovascular disease with advantages for patient diagnosis and treatment monitoring. Lower radiation is likely to be of particular value in the clinical imaging of younger patients but may also allow more complex research protocols investigating cardiovascular disease at multiple different time points with several different tracers. Magnetic resonance (MR)/PET is already being applied to the investigation of atherosclerosis and myocardial disease, although further research is required to

demonstrate its repeatability, precision, and cost-effectiveness. ^{18}F-FDG = ^{18}F-fluorodeoxyglucose; LGE = late gadolinium enhancement.

TABLE 1

Novel PET Tracers for Cardiovascular Applications

	Target	Disease	Ref. #
PET tracer			
^{18}F-Fluciclatide	αvβ3 and αvβ5 integrins	Angiogenesis/functional recovery post-myocardial infarction	(84)
^{11}C-hydroxyephedrine	Denervation in the myocardium	Ischemic heart disease/heart failure	(85)
^{11}C-PiB	Amyloid	Cardiac amyloidosis	(1)
^{18}F-florbetapir			
^{18}F-flutemetamol			
^{18}F-florbetaben			
^{64}Cu-DOTATATE ^{68}Ga-DOTATATE	Macrophages	Vascular inflammation in atherosclerosis	(86)
^{18}F-sodium fluoride	Micro-calcification	Atherosclerotic plaque and aortic stenosis	(10,14,19)
	Amyloid	Cardiac amyloidosis	(54)
^{18}F-MISO	Tissue hypoxia	Atherosclerotic plaque	(87)
^{68}Ga-NOTA-RGD	Angiogenesis	Atherosclerotic plaque	(88)
^{18}F-galacto-RGD			
^{11}C-PK11195	Translocator protein	Atherosclerotic plaque	(89)
^{11}C-choline ^{18}F-choline	Macrophages	Vascular inflammation in atherosclerosis	(90,91)
MR tracer			
Ultra-small paramagnetic iron oxide particles	Macrophages	Atherosclerotic plaque	(36,62)
Gadolinium-labeled liposomes	Monocytes	Atherosclerotic plaque	(92)
Paramagnetic quantum dots	Targeted cell internalization	Various targets: atherosclerotic plaque/ tumors	(93)
Gadolinium-labeled liposomes	Infarcted myocardium	Ischemic myocardium	(94)

MR = magnetic resonance; PET = positron emission tomography.

TABLE 2

Summary of the Characteristics of CT, MR, and PET Imaging and the Combined Modalities

	CT	MR	PET	PET/CT	MR/PET
Anatomic imaging					
Spatial resolution	Strong	Strong	Weak	Strong	Strong
Soft tissue contrast	Weak	Strong	NP	Weak	Strong
Molecular and functional imaging					
Molecular imaging	NP	NP	Strong	Strong	Strong
Exogenous contrast tissue imaging	Moderate	Strong	NP	Moderate	Strong
Tissue characteristics	Weak	Strong	NP	Weak	Strong
Temporal resolution	Moderate	Strong	Moderate	Moderate	Strong
Other					
Complexity	Strong	Moderate	Moderate	Moderate	Weak
Scan time	Strong	Weak	Moderate	Moderate	Weak
Cost	Strong	Moderate	Weak	Moderate	Weak
Robustness of imaging	Strong	Moderate	Moderate	Moderate	Weak
Potential					
Research potential	Moderate	Strong	Weak	Moderate	Strong
Translatability	Strong	Moderate	Weak	Strung	Moderate

CT = computed tomography; FDG = fluorodeoxyglucose; NP = not possible; other abbreviations as in Table 1.

TABLE 3

Summary of Potential Cardiovascular Uses of MR/PET

	MR Assessment	PET Assessment	Potential Clinical Use	Ref. #
Myocardial perfusion	Contrast-enhanced stress perfusion	^{82}Rb chloride, ^{13}N ammonia, ^{15}O water (stress perfusion)	Cross-validation Younger patients	(1)
Myocardial viability	LGE (myocardial tissue characterization)	^{18}F-FDG (viability)	Cross-validation Younger patients	(43,44)
Cardiac sarcoidosis	Cine imaging (LV structure and function) LGE and T1/T2 mapping (myocardial tissue characterization)	^{18}F-FDG, ^{68}Ga-dotatate (inflammation)	Assess disease activity Monitor response to therapy	(46–50)
Cardiac amyloid	Cine imaging (LV structure and function) LGE and T1 mapping (myocardial tissue characterization)	^{18}F-fluordide (TTR vs. AL amyloid) ^{18}F-fluorbetapan (amyloid deposition) ^{18}F-FDG (inflammation)	Differentiate AL from TTR amyloid Monitor response to therapy	(54)
Other cardiomyopathies	Cine imaging (LV structure and function) LGE and T1/T2 mapping (myocardial tissue characterization)	^{18}F-FDG, ^{68}Ga-dotatate (inflammation) ^{18}F-fluciclatide (angiogenesis) Novel tracers for fibrosis activity	Improve diagnostic accuracy Assess disease activity Monitor response to therapy	(48,51,67)
Atherosclerotic plaque	MR angiography (anatomy and stenosis) Multispectral black blood and T1-weighted plaque imaging (plaque burden and plaque characterization)	^{18}F-FDG, ^{68}Ga-dotatate (inflammation) ^{18}F-fluoride (microcalcification) ^{18}F-fluciclatide (angiogenesis)	Assess disease activity Monitor response to therapy Improve risk prediction	(57–64)
Heart valve disease	Flow mapping (severity of regurgitation/stenosis) Cine imaging (LV remodeling and function) LGE and T1 mapping (myocardial tissue characterization)	^{18}F-FDG, ^{68}Ga-dotatate (inflammation) ^{18}F-fluoride (microcalcification)	Simultaneous assessment of disease activity in the valve and LV remodeling Improve risk stratification Assessment of endocarditis	(15,68–70)
Congenital heart disease	Cine imaging (LV structure and function) Flow mapping (severity of regurgitation/stenosis)	^{18}F-FDG, ^{68}Ga-dotatate (inflammation) ^{18}F-fluoride (microcalcification)	Assess degeneration of prostheses Endocarditis	(7)
Aortic aneurysm disease	MR angiography (anatomy) USPIO imaging (inflammation) 4D flow mapping (shear stress mechanical stress)	^{18}F-FDG, ^{68}Ga-dotatate (inflammation) ^{18}F-fluoride (microcalcification)	Measure disease activity Improve risk prediction	(63)

4D = four-dimensional; AL = acquired monoclonal immunoglobulin light-chain; FDG = fluorodeoxyglucose; LGE = late gadolinium enhancement; LV = left ventricular; USPIO = ultra-small paramagnetic iron oxide; other abbreviations as in Tables 1 and 2.