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PET/MR in the assessment of non-ischemic heart disease

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Abbreviations:

CMR – cardiac MR; LGE – late gadolinium enhancement; PET – positron emission tomography; MR – magnetic resonance; CT – computed tomography; FLASH – fast low angle shot

1. Introduction

PET/MR has been utilized as an important medical imaging technology in clinical radiology for more than a decade. The introduction of the integrated PET and MR modalities has made it possible to simultaneously acquire high-resolution MR images with excellent soft tissue contrast [1-2] with metabolic PET images while minimizing ionizing radiation exposure to the patients. Furthermore, advances in improved attenuation correction [3-7] and MR triggered motion correction [8-11] have led to improved image quality, making PET/MR a preferred imaging modality [12].

Once such clinical application where PET/MR is particularly advantageous and shows potential for innovation is the assessment of non-ischemic cardiac disease [13]. Cardiac PET [14-15] allows for the assessment of cardiac viability or perfusion using different tracers. With evolving advanced MR imaging sequences, anatomic and functional analysis of the heart and large vessels has manifested in the form of high-definition cine sequences providing dynamic visualization of the heart and vascular structures. First-pass imaging of contrast medium transit through the myocardium has also been shown to depict stress-induced alteration in myocardial blood flow, differentiating between normal and hypo-perfused myocardium [16]. The accuracy of PET for the measurement of unmatched regions of myocardial perfusion, biomarkers and myocardial viability has further contributed to the increasing scope of applications for PET/MR imaging.

Of the different cardiac applications of PET/MR, the detection of presence and extent of myocardial fibrosis is one of relevance in various cardiac diseases. Both the PET and MR modalities in such cases can not only quantify the fibrosis, but also offer insight into early detection and prognostication of such underlying conditions. The aim of this article is to review the existing technologies and clinical examples of PET/MR imaging in the evaluation of four main non-ischemic causes of myocardial fibrosis, namely non-ischemic cardiomyopathies, cardiac amyloidosis, myocarditis and heart failure. All cardiac PET/MR studies were performed on a United Imaging Healthcare's uPMR® 790 system (United Imaging Healthcare, Shanghai, China).

2. Technical review of PET/MR technology

2.1 PET radiotracers

While ^{82}Rb-RbCl, ^{13}N-NH$_3$.H$_2$O and ^{15}O-H$_2$O are the common radiotracers utilized in PET perfusion, there have been newer PET imaging agents being studied for various cardiac applications. Table 1 summarizes these novel cardiac PET imaging radiotracers, and their target disease processes.

Table 1. summary of novel PET radiotracers in evaluation of cardiac disease.

Target disease process	Cardiac PET radiotracers
Perfusion	^{13}N-NH$_3$, H$_2$O, ^{82}Rb, ^{15}O-H$_2$O, ^{18}F-flurpiridaz
Myocardial sympathetic nerve activity	^{11}C-hydroxyephedrine, ^{18}F-LMI1195
αvβ3 and αvβ5 integrins in angiogenesis or post myocardial infarction reperfusion	^{18}F-Fluciclatide
Cardiac amyloid	^{11}C-PIB, ^{18}F-florbetapir, ^{18}F-flutemetamol, ^{18}F-florbetaben
Fibrosis	^{68}Ga-FAPI, ^{18}F-FAPI
Atherosclerotic microcalcification	^{18}F-NaF
Tissue hypoxia	^{18}F-MISO, ^{18}F-HX4, ^{64}Cu-ATSM, ^{64}Cu-CTS
Angiogenesis	^{68}Ga-NOTA-RGD, ^{18}F-galacto-RGD
Macrophage-dependent inflammation	^{68}Ga-pentixafor, ^{64}Cu-DOTATATE, ^{68}Ga-DOTATATE, ^{89}Zr-DNP

2.2 CMR sequence technology

Table 2 summarizes the commonly used MRI sequences in the anatomic, functional, and biochemical characterization of myocardial tissue. As described in the applications below, these sequences provide information on early and late stages of various non-ischemic conditions [17].

Table 2. summary of commonly used sequences in the assessment of myocardial tissue and the relevant applications or findings.

Specific CMR sequence	Relevant application/finding
CINE T1W	Function, anatomical details, fat
Black Blood T2W	Anatomical details, edema
T1 mapping	Fibrotic areas (regional or diffuse), amyloidosis, fat
T2/T2* mapping	Edema, iron
ECV mapping	Fibrotic areas (regional or diffuse), amyloidosis
Late gadolinium enhancement	Fibrotic areas (regional fibrosis), viability

2.3 PET/MR cardiac image registration

The main challenge for cardiac PET in clinical practice is the compensation of physiologic motion, such as respiratory and cardiac motion, for which a few methods have been developed to overcome the problem [18-20] including a two-stage cardiac PET and LGE co-registration method (Figure 1) [21].
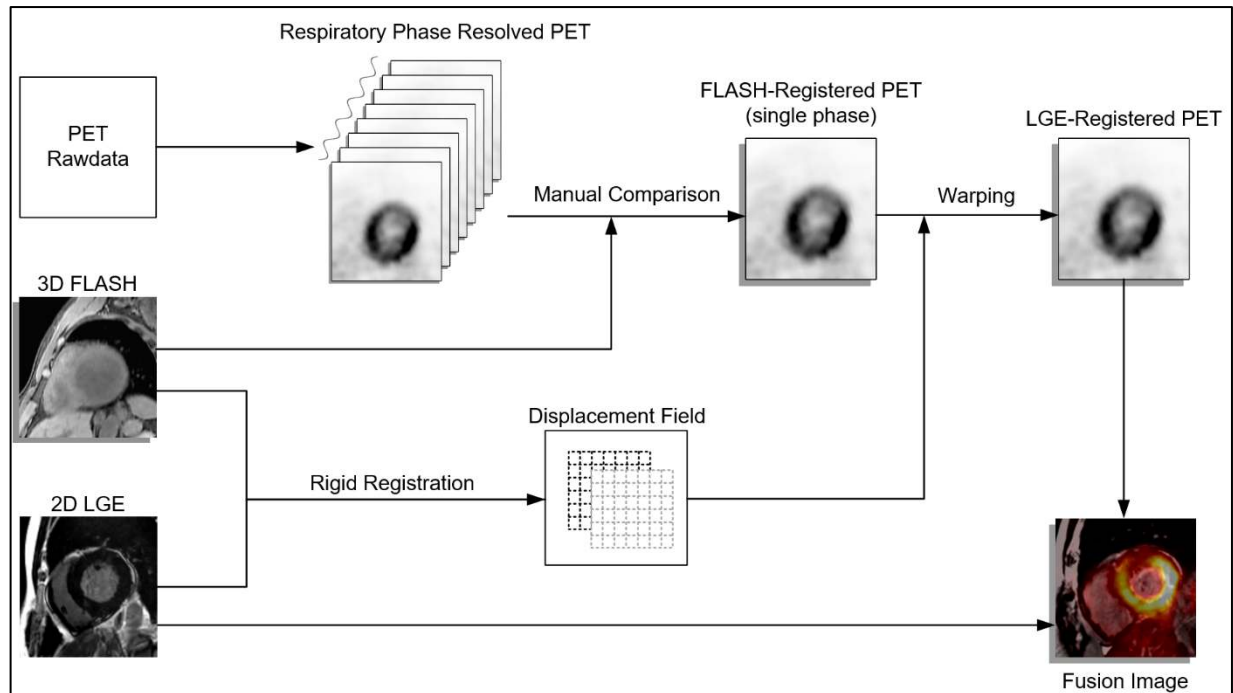
Figure 1. Two-stage cardiac PET and MR LGE co-registration method.

Figure 1 is an illustration of image co-registration of LGE and PET with two-stage registration. This comprises of four stages. The first is binning of list-mode PET data into eight respiratory bins based on respiratory signal. The second step is comparison of FLASH and respiratory phase resolved PET to choose one FLASH-registered phase. Thirdly, rigid registration is manually performed between 3D FLASH and 2D LGE and get the 3D displacement field. Finally, the displacement field is used to warp the images and generate LGE-registered PET.

3. Non-ischemic cardiomyopathies – hypertrophic and dilated cardiomyopathies

Non-ischemic cardiomyopathies are defined as diseases of the myocardium associated with mechanical or electrical dysfunction exhibiting inappropriate ventricular hypertrophy or dilatation and include dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM). Causes include primary and secondary causes, encompassing genetic and acquired factors. CMR remains the main diagnostic tool for distinguishing many of these diseases; however, for certain diseases, PET can add valuable information by characterizing metabolic activity in the myocardial region.

LGE sequence can detect focal myocardial fibrosis and provide significant risk stratification for sudden cardiac death, mortality, and heart failure hospitalization in patients with non-ischemic cardiomyopathy [22]. The combination of metabolic information from ^{18}F-fluoro-deoxy-glucose PET (^{18}F-FDG PET) and LGE can also provide additional evidence for the evaluation of myocardial viability and inflammation in non-ischemic cardiomyopathies.

Case Example

A 67-year-old male patient with known dilated cardiomyopathy (DCM) was evaluated for myocardial viability assessment. ^{18}F-FDG PET/MR was performed at an uptake time of 60 minutes. Figure 2 shows short axial LGE images (A, C) and LGE/PET fusion images (B, D) of two LGE-enhanced lesions.
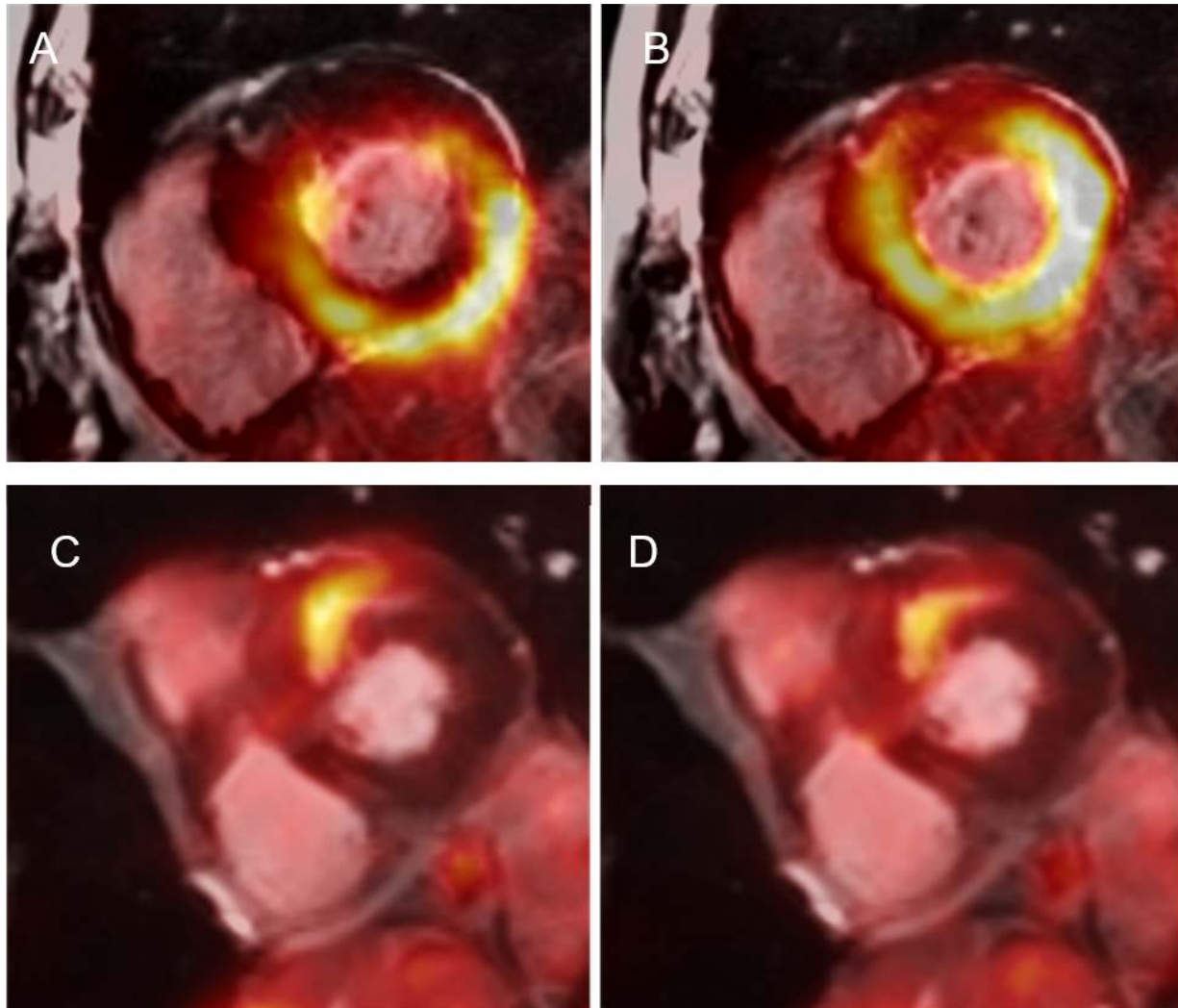
Figure 2. PET/MR images of a patient with dilated cardiomyopathy (DCM). Short axial LGE images (A, C) and LGE/PET fusion images (B, D) show two LGE-enhanced lesions.

4. Cardiac amyloidosis (Restrictive cardiomyopathy)

Cardiac amyloidosis is a myocardial condition characterized by extracellular amyloid infiltration throughout the heart and is the leading cause of morbidity and mortality in systemic amyloidosis. The two types of amyloid that commonly infiltrate the heart include acquired monoclonal immunoglobulin light chain amyloid (AL) and transthyretin-related (familial and wild-type/senile) amyloid (ATTR). Differentiation of the two types is important because they have different prognoses and are amenable to different management strategies.

Early cardiac amyloidosis is challenging to diagnose and may only present with the features of right-sided congestive heart failure in advanced disease. While endocardial biopsy is considered the gold standard for diagnosis of cardiac amyloidosis, it is not commonly used due to its high rate of complications. Other non-invasive diagnostic methods used include electrocardiography, echocardiography, CMR and nuclear medicine imaging.

Steady state free precession cine sequences in CMR are used to assess cardiac function and structure, while LGE imaging can diagnose cardiac amyloidosis. Although CMR is sensitive and specific for cardiac amyloidosis, CMR classically cannot differentiate the subtypes of cardiac amyloidosis and PET imaging is useful in this regard. However, recent studies have shown that AL frequently manifests as diffuse subendocardial LGE, while ATTR typically manifests as transmural LGE. MR parametric

mapping has also shown that the T1 value of ATTR patients was significantly higher than that of hypertrophic cardiomyopathy and normal controls, but not as high as that of AL patients, further helping in the characterization of cardiac amyloidosis.

Nuclear medicine imaging plays an important role in the diagnosis, classification, prognostic evaluation, and therapeutic response monitoring of myocardial amyloidosis [23-24]. Studies using ^{18}F-NaF PET imaging [25-26] have shown that the myocardial uptake in ATTR patients is higher than AL patients and control groups, and the myocardial radioactivity uptake was consistent with the extent of damaged myocardium as seen on MR LGE. Similar studies have shown differences in uptake using ^{18}F-florbetapir and ^{18}F-florbetaben imaging in both ATTR and AL patients [27-28]. Hence, an important benefit of combining PET with CMR is the combination of quantifiable parameters to potentially aid prognosis and track disease progression.

Case Example

A 65-year-old female with underlying history of amyloidosis presented with chest congestion and dyspnea. Echocardiography revealed pericardial effusion, pleural effusion, interventricular septum and left ventricular wall thickening. Gadolinium contrast enhanced CMR and dynamic cardiac PET imaging (Figure 3) was performed immediately after injection of ^{18}F-florbetapir (AV45). CMR imaging revealed LV hypertrophy and impaired systolic function (LVEF=22%). LGE imaging (B, short axis view; E, 4 chamber view) demonstrated transmural late enhancement in the left ventricle. Delayed whole body maximum intensity PET (A, 90min post-injection) demonstrated elevated AV45 uptake in heart (SUVmax=8.86), lung (SUVmax=2.69) and spleen (SUVmax=7.75), compared to moderate uptake in the liver (SUVmax=3.09) caused by hepatobiliary excretion of the drug.
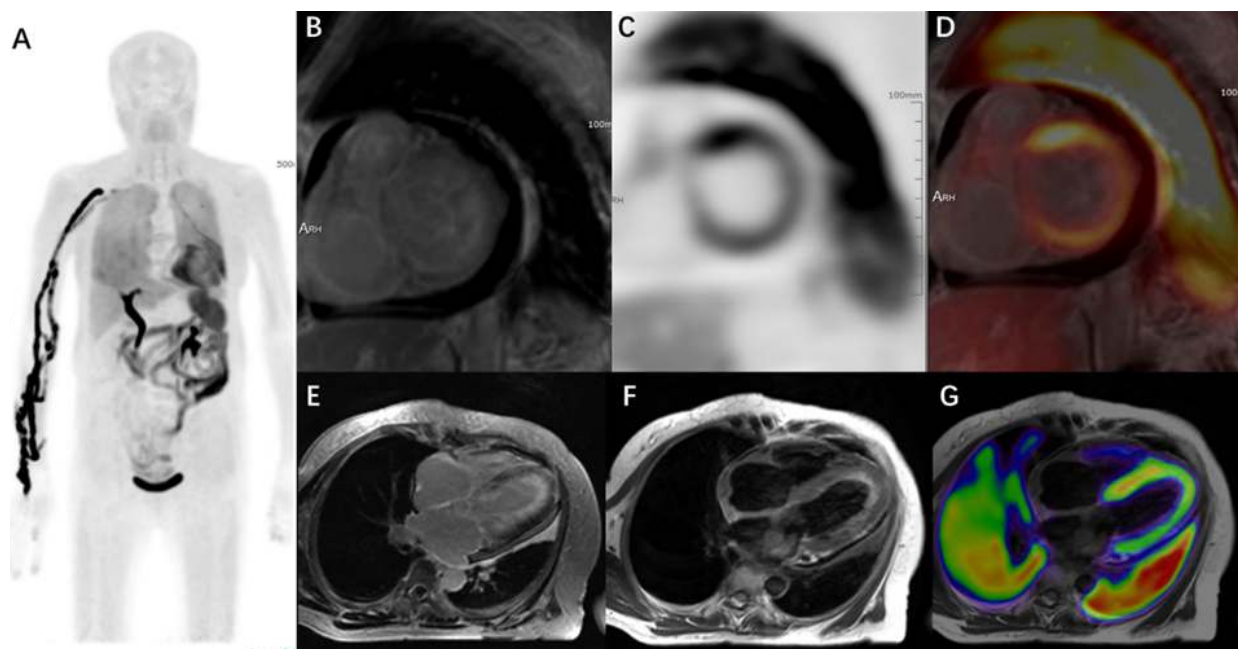

Figure 3. PET/MR images of a patient with cardiac amyloidosis.

5. Myocarditis

Myocarditis is an inflammatory disease of the myocardium that can be caused by various conditions including viral infections, autoimmune reactions, toxin exposure, drugs, and idiopathic factors [29].The condition has a predilection in young subjects, especially males [30]. Clinical symptoms are highly variable, making diagnosis challenging. In addition, investigations such as laboratory biomarkers (such as troponin, C-reactive protein), electrocardiography and echocardiography are nonspecific. Definite diagnosis relies on endomyocardial biopsy but this is not performed

frequently in practice due to its risk of complications.

Pathophysiological processes linked to myocardial inflammation, including myocardial hyperemia and edema in the early stages, and fibrosis or scarring in the later stages, as well as associated processes such as pericardial effusion and global or regional wall motion abnormalities, can be assessed using MR imaging [31]. The Lake Louise CMR criteria often used in assessment of myocarditis encompasses the three aspects of myocardial inflammation namely edema, hyperemia and necrosis and/or fibrosis. In addition to these, multiparametric T1 and T2 mapping can also be used for tissue characterization.

The use of ^{18}F-FDG PET [32] allows accurate assessment of the extent and grade of both active and healed inflammatory processes. FDG uptake in myocarditis could be focal, diffuse, or 'focal on diffuse' depending on the underlying disease [33]. Thus, ^{18}F-FDG PET/MR imaging has already been shown to be highly clinically relevant in patients with suspicion of myocarditis, with increasing evidence that ^{18}F-FDG PET/MR imaging can diagnose, grade, and monitor myocarditis [34-36], with a clinical sensitivity of 74% and a specificity of 97% [37]. Notably, it has also been

shown that patients with biopsy-proven myocarditis have had abnormal uptake noted on ^{18}F-FDG PET imaging, while having no corresponding evidence of myocardial damage on MR imaging, allowing for early diagnosis of myocarditis. Performing FDG PET imaging after treatment could also show interval improvement or resolution of the abnormal FDG uptake, highlighting further potential application in monitoring treatment response [38].

Case Example

A 24-year-old male presented with signs and symptoms suggestive of myocarditis. Gadolinium contrast enhanced CMR and dynamic cardiac PET imaging starting immediately after injection of ^{18}F-FDG (Figure 4). CMR imaging showed normal anatomy of the atrioventricular chambers with normal left ventricular motion and function (LVEF 70%). Delayed enhancement imaging showed blurred patchy, slightly high signal and line-like high signal in the basal segment of the anterior and inferior lateral walls of the left ventricle, and no obvious abnormal enhancement was found in the remaining ventricular wall segments. Myocardial metabolic imaging revealed increased radioactive uptake in each segment of the left ventricle.
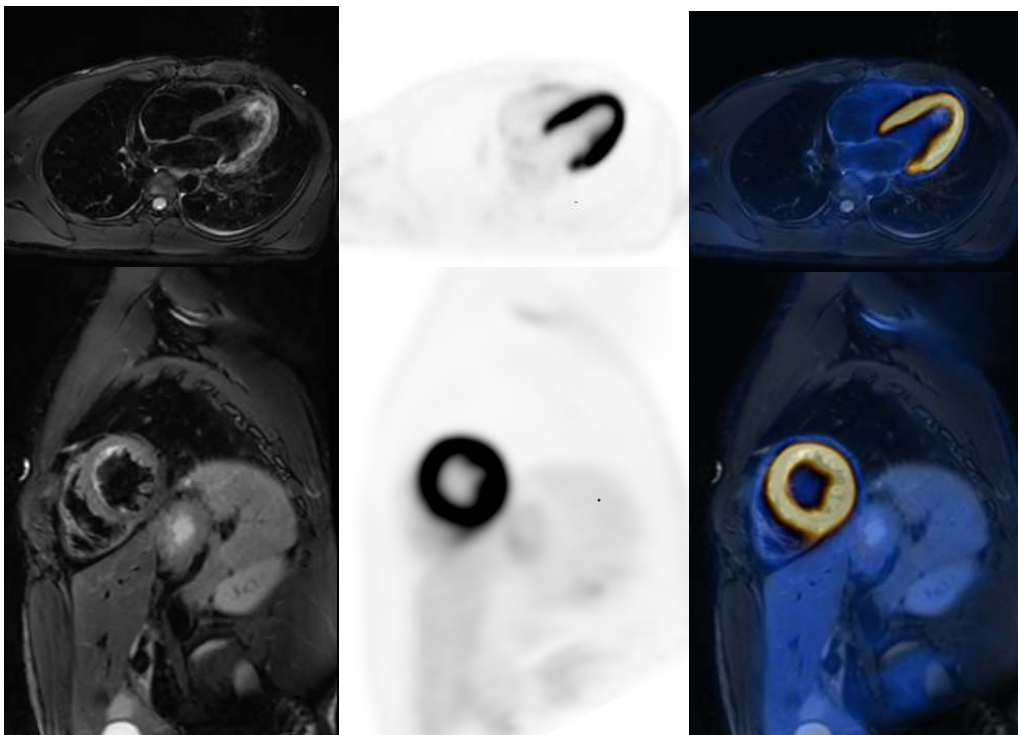

Figure 4. PET/MR images of a patient with myocarditis.

6. Heart Failure

Heart Failure is defined as a complex clinical syndrome resulting from any structural or functional cardiac condition that impairs the ability of the ventricle to fill or eject blood [39]. Several criteria have been proposed to diagnose heart failure such as the Framingham criteria [40]. Echocardiography is frequently used to provide information on the ventricular ejection fraction as well as the underlying cause of heart failure. Single-photon-emission computed tomography (SPECT) remains the most common imaging modality used for myocardial perfusion imaging in heart failure, but it has significant disadvantages such as limited resolution and involves the use of ionizing radiation. Due to these factors, there has been increasing use of myocardial perfusion imaging using PET to quantify myocardial blood flow using tracer kinetics, for which the sensitivity and specificity is thought to be approximately 90% [41-44]. It is also notable that a meta-analysis of single and multi-center studies confirmed the excellent sensitivity and specificity of CMR to quantify myocardial perfusion at rest and during stress [43-44][4]. There is report showing that MR perfusion imaging is compared to that of SPECT and showed significant agreement in results with PET perfusion [45-46][-46]. The combination of PET and MR imaging allows for direct comparison of myocardial blood flow under resting and stress conditions. The assessment of myocardial viability is a standard approach utilized in patients with advanced coronary disease or who are in early or advanced states of heart failure. Identification of glucose utilization in viable myocardium by PET is made possible by FDG uptake demonstrated in myocardial segments with decreased

perfusion. Based on meta-analyses, ^{18}F-FDG PET predicts functional recovery after revascularization with a sensitivity of 92% and a specificity of 63% [47-48]. LGE also allows the identification of scarred myocardium as signal enhanced areas.

Case Example

Figure 5 shows an example of ^{68}Ga-FAPI and FDG PET imaging of a 77-year-old male with history of coronary artery disease, that presented with acute pulmonary embolism. Echocardiography showed severe pulmonary hypertension (pulmonary artery systolic blood pressure elevated at 99mm Hg), right atrioventricular enlargement, as well as decreased right ventricular motion and function, with normal left ventricular systolic function. Pulmonary angiography and balloon angioplasty was performed and revealed multiple filling defects in the bilateral pulmonary arteries with poor distal perfusion. Gadolinium contrast enhanced CMR and dynamic cardiac PET imaging starting immediately after injection of ^{68}Ga-FAPI was performed (Figure 5). Gadolinium contrast enhanced CMR and dynamic cardiac PET imaging starting immediately after injection of FDG was performed the following day. CMR showed right atrial and ventricular enlargement and hypertrophy as seen in the 4-chamber and short axis views. ^{68}Ga-FAPI PET/MR imaging showed diffusely increased FAPI uptake in the right atrial muscle wall and increased scattered patchy FAPI uptake in the right ventricular muscle wall. ^{18}F-FDG PET/MR fusion images demonstrated that radioactivity uptake in the right ventricle and atrium were increased, more so in the right ventricle.
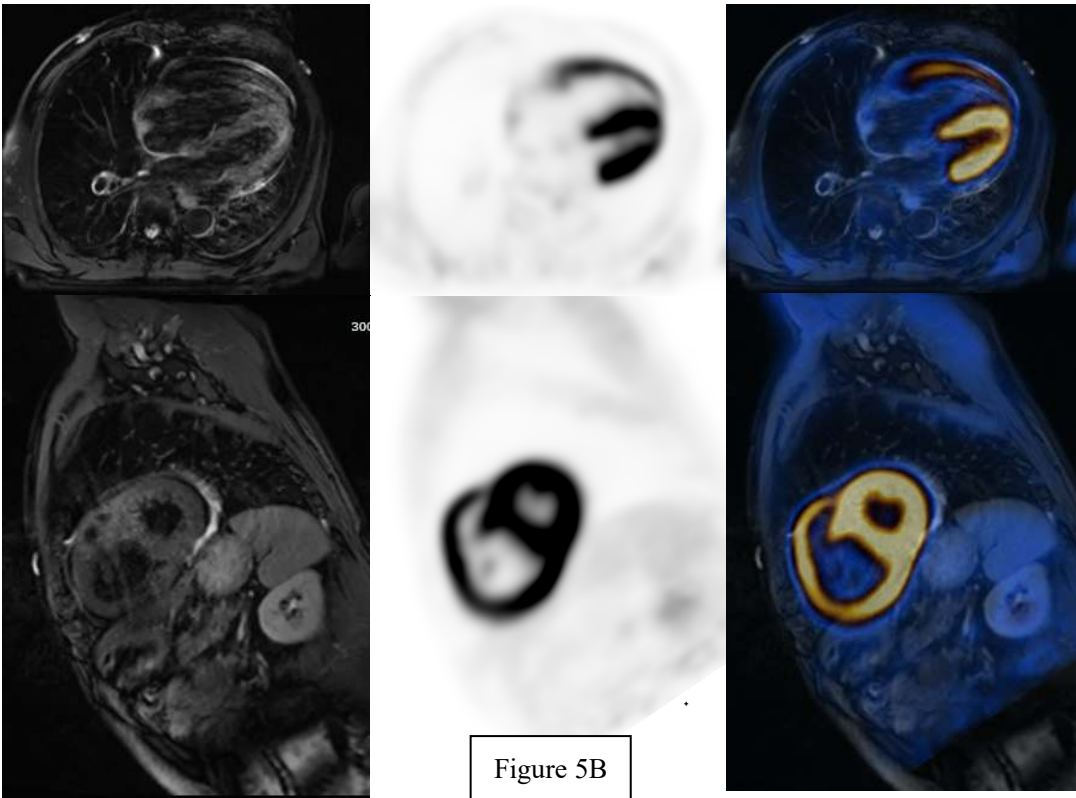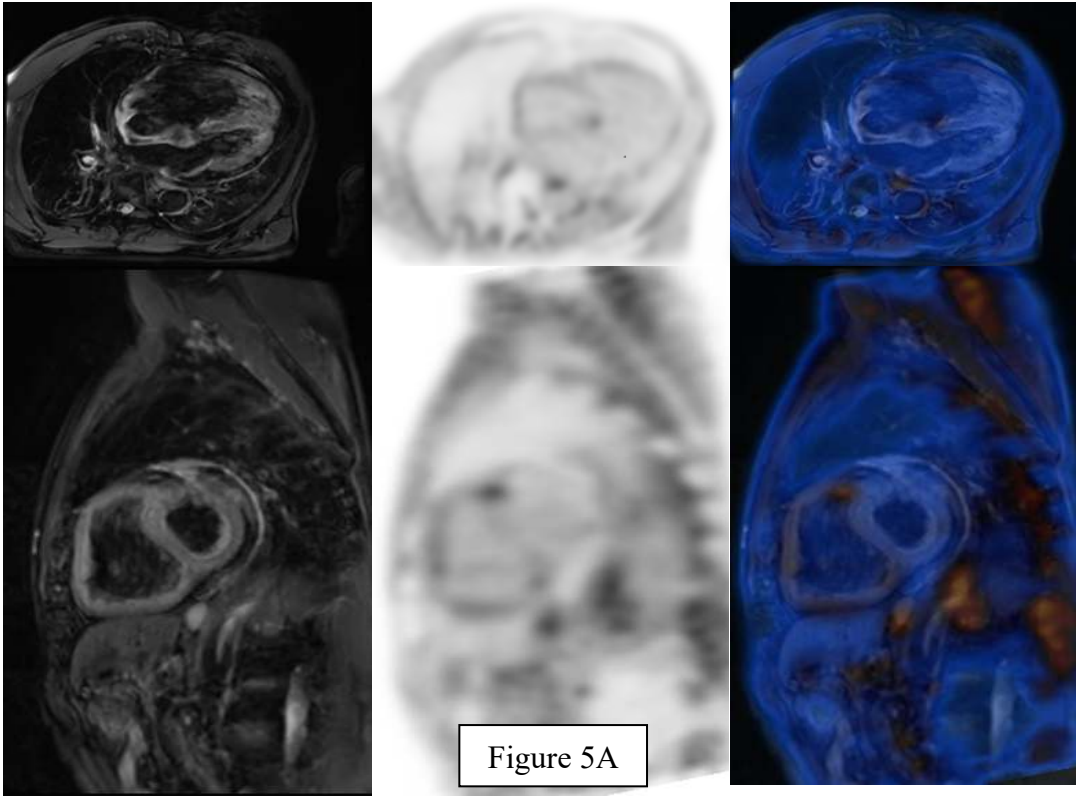
Figure 5A

Figure 5B

Figure 5. ^{68}Ga-FAPI and FDG PET/MR images of a patient with heart failure and extensive fibrosis.

7. Conclusion and Future Directions

Currently, there are three vendors providing PET/MR integrated scanners worldwide: Siemens Biograph mMR (2010), GE SIGNA (2013) and United Imaging Healthcare's **uPMR**® 790 (2017). The hybrid MR and PET imaging has demonstrated its clinical advantage in many cardiac applications and is increasing used in clinical routine imaging. Some disadvantages to this advancing technology exist, including the high cost of PET/MR exams and the complex technology requiring significant training in both PET and MR technology for technologists to run the scans. In addition, several cardiac devices including pacemakers, implantable cardioverter-defibrillators, and mechanical heart valves, as well as some coronary stents, are contraindications to PET/MR scans. However, with further improvements in PET/MR imaging technology and more studies evaluating the use of new imaging tracers, there is an exciting potential to harness the advantages of PET/MR in evaluating different cardiac diseases. Prospective single-center and multi-center study with large sample size are urgently needed to further explore the indications and new application area of integrated PET/MR.

8. Image/Figure Courtesy

All images are the courtesy of Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China.

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