Combined ^{18}F-FDG PET/MR for Enhanced Imaging of Active Cardiac Sarcoidosis

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Introduction

Sarcoidosis is a multisystem disease characterized by granuloma formation, inflammation and fibrosis most commonly affecting the lungs and mediastinal lymph nodes [1]. Cardiac involvement is under-diagnosed but is the leading cause of death amongst patients with sarcoidosis [2–6]. Early intervention with steroids appears to improve prognosis [7], making the accurate and early diagnosis of subclinical but active cardiac sarcoidosis an important clinical goal. Unfortunately establishing this important diagnosis remains a major clinical challenge [8, 9].

Cardiac magnetic resonance (MR) imaging with late gadolinium enhancement (LGE) has recently been introduced for visualizing the pattern of myocardial injury due to cardiac sarcoidosis [10, 11]. However, LGE cannot differentiate between active disease and old chronic scarring, thus limiting the specificity of CMR-based active sarcoidosis assessments. On the other hand, positron emission tomography (PET) imaging with ^{18}F-Fludeoxyglucose (^{18}F-FDG)[1], has recently been used to identify regions of increased myocardial inflammation in patients with active cardiac sarcoidosis [12–14]. However, glucose is the predominant source of energy consumed by the myocardium, and high non-specific physiological uptake of ^{18}F-FDG can often lead to false positive identification of active myocardial disease. Although dietary restrictions in the 12 hours prior to PET imaging may switch the heart from glucose to free-fatty acid metabolism and effectively suppress physiological ^{18}F-FDG uptake in the myocardium, this strategy is not always successful [14–16].

Recently, hybrid PET/MR systems have become clinically available [17–19]. The simultaneous hybrid PET/MR Biograph mMR system (Siemens Healthcare, Erlangen, Germany) combines a sensitive PET scanner with a 3T MR system to enable spatial co-registration of complementary imaging data from the two modalities [20]. Simultaneous acquisition of PET and MR data allows disease activity measured by PET to be precisely overlaid on the pattern of injury in the myocardium determined by MR from a single scan session [21]. Moreover, by replacing CT with MR, PET/MR is associated with a lower radiation dose, which is important, especially in chronic conditions such as cardiac sarcoidosis, where follow-up would be desirable [17].

Recent studies in our institution have investigated the use of MR/PET for evaluating cardiac disease [21, 22] including cardiac sarcoidosis by assessing the overlap between ^{18}F-FDG PET activity and the pattern of myocardial injury on LGE MR. We have investigated the potential of combined PET/MR to differentiate between active and inactive cardiac sarcoid as well as identifying false-positive PET indications, due to inadequate physiological ^{18}F-FDG myocardial uptake suppression [22, 23].

[1] The full prescribing information for the Fludeoxyglucose F18 injection can be found at page 37.

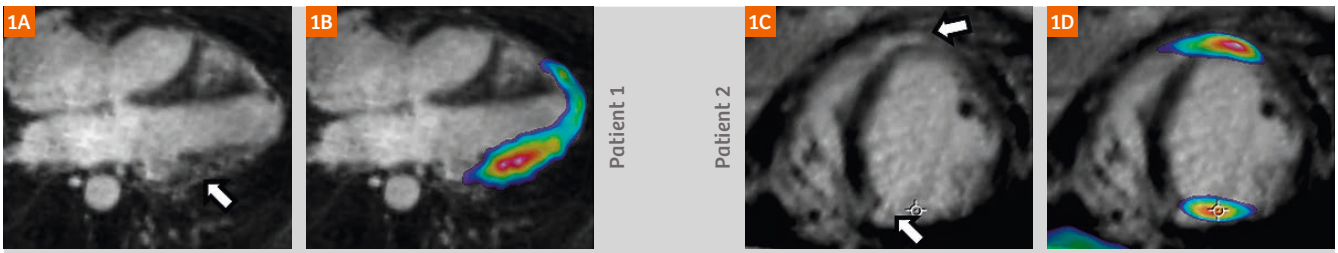

Figure 1: From left to right: **(1A, C)** LGE MR images showed elevated LGE signal at the lateral and anteroseptal wall for patient 1 (62-year-old male) and patient 2 (63-year-old female) respectively. **(1B, D)** Matched ^{18}F-FDG PET fused with previous LGE MR images showed high ^{18}F-FDG uptake overlapping with the LGE pattern of injury.

Optimized PET/MR imaging protocol for cardiac sarcoidosis assessment

In this article, we present four clinical exams where initial diagnosis for active cardiac sarcoidosis was unclear when either LGE MR or ^{18}F-FDG PET exams were evaluated independently [22, 23]. All participating subjects had a previous history of proven extra-cardiac sarcoidosis and/or clinical symptoms to suggest cardiac sarcoid involvement. Patients gave written informed consent and were screened for contra-indications before undergoing PET/MR imaging.

Dynamic PET data were acquired across a single bed position centered over the heart in list mode for a period of 90 min beginning 10 min after 5 MBq/kg ^{18}F-FDG injection. The collected PET data were then histogrammed into a single scan time window corresponding to a delayed 40–100 min post-injection period. Subsequently the PET data were reconstructed with an iterative ordinary Poisson Ordered Subset Expectation Maximization (OP-OSEM) algorithm using 3 iterations, 21 subsets and a resolution modeling method optimized for the Biograph mMR system. An MR-based attenuation correction method was employed for the PET data based on 4-tissue class segmentation of a standard breath-hold 3D Dixon VIBE MR sequence. Attenuation from the body transmit coil and spine array, but not from the flexible chest array, were included in the attenuation map.

Cardiac MRI, performed simultaneously with the dynamic PET acquisition, included

i) TrueFISP cine images, acquired in the long-axis (2-chamber, 4-chamber) of the left ventricle, followed by

ii) a complete short-axis stack for assessment of cardiac volume and function, and

iii) inversion recovery-prepared spoiled gradient echo late gadolinium enhanced imaging, 10–15 minutes post injection of 0.2 mmol/kg Multi Hance (Bracco imaging, Milan, Italy) in short- and long-axis views [24]. Inversion times were optimized to null normal myocardium with images repeated in two separate phase-encoding directions to exclude artifact.

Enhancing cardiac sarcoid diagnosis with simultaneous PET/MR imaging

In patients 1 and 2, elevated ^{18}F-FDG uptake (at later times >60 min post tracer injection) co-localized with the pattern of late gadolinium enhancement observed on MRI (Fig. 1). The coincidental observation of both increased ^{18}F-FDG-PET activity and evidence of myocardial injury on late gadolinium enhancement strongly suggests the presence of active cardiac sarcoidosis. Target-to-background (TBR) values were calculated as mean standard uptake values (SUV) in regions-of-interest (ROI) drawn over the area of myocardial injury divided by the mean blood pool SUV value in the left ventricular cavity. Mean ^{18}F-FDG TBR in areas of myocardial injury were 2.2 (patient 1) and 2.0 (patient 2).

Conversely, overlap of PET and LGE was not observed in patients 3 and 4 (Fig. 2). In patient 3 transmural scarring in a coronary distribution affecting the anteroseptum was observed on LGE MR but with no evidence of increased ^{18}F-FDG PET uptake in this region. This finding was felt to be consistent with a chronic and silent myocardial infarction. By contrast, patient 4 demonstrated avid and diffuse ^{18}F-FDG uptake throughout the entire left ventricular myocardium in the absence of any evidence of myocardial injury on LGE MR. Given that cardiac sarcoidosis is a focal disease process this was felt likely to represent failed suppression of the physiological ^{18}F-FDG uptake [25]. This hypothesis was supported by the very high TBR values (6.3 60–90 min post injection) in this patient compared to subjects 1 and 2. However, more evidence is needed to be able to differentiate the true- from the false-positive cardiac sarcoid ^{18}F-FDG assessments in the absence of positive LGE MR signal.

Future prospects for cardiac PET/MR imaging

This preliminary study has demonstrated the clinical potential of simultaneous PET/MR imaging in the evaluation of active cardiac sarcoidosis. PET and MR images can be accurately aligned allowing a diagnosis of active cardiac sarcoidosis to be made with confidence when increased

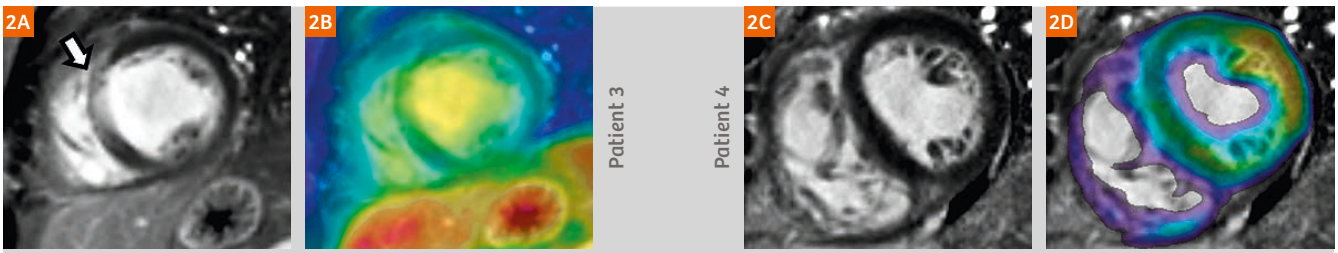

Figure 2: (2A, B) Patient 3 (50-year-old female), short-axis LGE MR showed transmural LGE on the anteroseptum, while fused PET/MR images demonstrated absence of high ^{18}F-FDG uptake on the same region. **(2C, D)** Patient 4 (42-year-old male) LGE MR showed absence of LGE on the myocardial wall. Fused PET/MR images indicated diffused intense ^{18}F-FDG uptake.

^{18}F-FDG uptake co-localizes with the pattern of injury on late gadolinium enhancement MRI. Moreover this approach can help differentiate this pattern from non-active cardiac sarcoid LGE signal or false positive ^{18}F-FDG uptake due to failed myocardial suppression.

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