

Prevalence of ¹⁸F-Fluorodeoxyglucose Positron Emission Tomography Abnormalities in Patients with Arrhythmogenic Right Ventricular Cardiomyopathy

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Keywords

Arrhythmogenic right ventricular cardiomyopathy; cardiac magnetic resonance imaging; 18F-fluorodeoxyglucose; positron emission tomography; myocarditis.

Structured Abstract

Background

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a heritable heart muscle disease that causes sudden cardiac death in the young. Inflammatory myocardial infiltrates have been described at autopsy and on biopsy, but there are few data on the presence of myocarditis in living patients with ARVC using non-invasive imaging techniques. FDG-PET is a validated technique for detecting myocardial inflammation in clinically suspected myocarditis. We aimed to determine the prevalence of myocardial inflammation in patients with ARVC using ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET).

Methods and Results

We performed a retrospective analysis of a single centre cohort of patients with ARVC referred for FDG-PET scans between 2012 and 2017 for investigation of symptoms or suspected device infection. Sixteen patients (12 male; age 42±13 years) with a definite diagnosis of ARVC were identified. Seven had positive FDG-PET scans, two of whom had cardiac sarcoidosis on endomyocardial biopsy. Of the remaining five, two carried pathogenic desmoplakin mutations. FDG uptake was found in the left ventricular myocardium in all cases. One patient also had right ventricular uptake.

Conclusion

In this exploratory study, we show that some patients with ARVC have evidence for myocardial inflammation on FDG-PET, suggesting that myocarditis plays a role in disease pathogenesis.

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare heart muscle disorder that causes sudden cardiac death in young asymptomatic people [1]. Histologically, it is defined by myocardial cell death and fibrofatty replacement, but inflammatory myocardial infiltrates are also reported in 60-80% of post-mortem/transplant cardiac specimens [2-6]. Although reports from biopsies in these patients have described inflammatory infiltrates, studies examining myocardial inflammation *in vivo* using non-invasive techniques are lacking [7]. The relevance of myocardial inflammation to the pathogenesis and clinical phenotype of ARVC is unknown.

¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) is an established method for detecting and assessing myocardial inflammation and is used in our centre for the assessment of suspected myocarditis [8]. In this study, we performed a retrospective analysis of patients fulfilling current diagnostic criteria for ARVC who also underwent FDG-PET to test the hypothesis that myocardial inflammation plays a role in disease pathogenesis.

Methods

Study population

The study cohort comprised patients with ARVC referred for FDG-PET between 2012 and 2017. The inclusion criteria were a definite diagnosis of ARVC using the 2010 revised Task-Force Criteria [9] and a complete clinical workup consisting of electrocardiogram (ECG), signal-averaged ECG, transthoracic echocardiogram and/or cardiac magnetic resonance (CMR). All patients had an established ARVC diagnosis prior to FDG-PET scanning. Patients with a positive FDG-PET scan were referred for an endomyocardial biopsy unless there was a clear familial/genetic background explaining the clinical phenotype. The study was conducted in accordance with institutional guidelines and the declaration of Helsinki.

FDG-PET protocol and image analysis

All patients underwent dietary preparation for 24 hours prior to PET scanning using a high-fat diet and avoidance of carbohydrates, sugars, dairy and starchy foods followed by a prolonged fast for 12 hours to suppress physiological myocardial FDG uptake. Adherence was confirmed through direct questioning. Before tracer administration, patients received 50 IU/kg unfractionated intravenous heparin. A weight-based dose of the radiopharmaceutical ^{18}F -FDG was administered intravenously (mean activity of 370MBq; dose reference level 400MBq; effective dose 8mSv) followed by a rest period using a standard clinical protocol [8]. One hour following the intravenous administration of ^{18}F -FDG patients underwent whole-body, supine, resting metabolic imaging using a 64- slice GE Discovery DVCT PET scanner (GE Healthcare Systems, Waukesha, WI, USA). An initial scout scan (using a tube potential of 120kV and current of 10mA) followed by a high-resolution computed tomography (HRCT) scan of the thorax was acquired on full inspiration. The HRCT scan parameters comprised a detector coverage of 40mm, field of view of 50cm (FOV), helical collimation (slice thickness) of 1.25mm, pitch of 0.516mm/rotation at a rotation speed of 0.7sec (with coverage speed 29.5mm/sec). The computed tomography (CT) exposure factors comprised a tube potential of 100kVp, current of 200mA and rotation time of 0.7s. While maintaining patient position, a CT for attenuation correction was performed using 64 detectors, a pitch of 1.375, and 2.5 mm collimation (slice thickness). A simultaneous non-ECG gated, whole-body PET scan was acquired in 3D-mode. PET data was collected for 2 minutes at each bed position from the skull to mid-thigh covering the area identical to that taken during the CT and using similar collimation parameters.

PET images were reconstructed using CT for attenuation correction and re-orientated into standard views. Each image set was displayed as colour images with an SUV range from 0 – 10. Whole body, trans-axial, emission images of 4.3 mm × 4.3 mm × 4.25 mm and fused cardiac short axis and horizontal long axis image stacks along with vertical long axis for visual image interpretation, were iteratively reconstructed using ordered-subsets expectation maximization with 20 subsets and 2 iterations, a Gaussian filter with 6mm full width at half maximum, a 128 x 128 image matrix with zoom of 1 and an axial field of view of 70cm.

PET images were analysed qualitatively. Left ventricular myocardial FDG uptake was categorised visually into 4 patterns: ‘none’, ‘diffuse’, ‘focal’ and ‘focal on diffuse’. Focal or focal- on-diffuse was categorised as a positive scan and none or diffuse uptake as a negative scan [10]. The presence or absence of focal FDG uptake within the right ventricular (RV) free wall was also recorded. Each scan was assessed for the presence of extracardiac disease including lymphadenopathy, lung parenchymal, solid visceral or bony abnormalities.

Endomyocardial biopsy

Endomyocardial biopsy (EMB) was performed by experienced clinicians via the jugular or femoral vein. Either left or right ventricular sampling was performed based on the clinical presentation. The endomyocardial biopsy samples were formalin fixed and processed to paraffin wax. Sections of the paraffin-embedded tissue were cut at three levels at 4 micrometres thickness and stained with haematoxylin and eosin. Mononuclear cell interstitial infiltrates were specifically sought, together with evidence of myocyte necrosis. Sections were stained immunohistochemically with antibodies to CD3, CD68 and HLA-DR. A connective tissue stain (Masson trichrome) was employed to assess interstitial fibrosis.

Statistical Analysis

Summary descriptive statistics are reported as mean \pm SD or frequency counts (%) for continuous and categorical variables, respectively. Categorical variables were compared between groups using the chi-square or Fisher's exact test as appropriate. Continuous variables were compared using the Mann–Whitney U-test. Reported p-values are two-sided. All statistical tests were performed at the 5% level of significance. SPSS 25.0 software (SPSS, Chicago, IL, USA) was used for all analyses.

Results

Sixteen patients with a definite ARVC diagnosis underwent FDG-PET imaging between 2012 and 2017. The indications for the FDG-PET scan were: clinically suspected myocarditis (n=7); suspicion of cardiac sarcoidosis (n=5); worsening systolic function (n=2); and investigation for suspected implantable device infection (n=2).

Seven patients underwent endomyocardial biopsy. This revealed cardiac sarcoidosis in 2 patients (Supplementary Figure 1). Histology in the remaining five patients demonstrated no evidence for myocardial inflammation. FDG-PET scanning preceded the EMB by 1, 10, 20 and 20 weeks for cases 1, 3, 4 and 5, respectively. Biopsy was performed prior to FDG-PET scanning in case 9 as part of the initial diagnostic workup.

None of the FDG-PET scans, including those in patients with histologically proven sarcoid, demonstrated extra-cardiac uptake. Of the two patients with histological evidence for sarcoidosis, one had a positive FDG-PET scan with focal left ventricular (LV) uptake and the other had diffuse LV uptake (Supplementary Figure 1). These cases have been excluded from further analysis. Of the remaining 14 patients (10 male; age 41.7 ± 13.8 years), 5 (36%) had a

positive FDG-PET scan (Figures 1-3, Supplementary Figure 2): 4 had focal LV uptake and one had diffuse LV uptake with focal uptake in the RV, which was considered a positive scan. Their diagnostic features are presented in supplementary table 1. Clinical characteristics of the FDG-PET positive and negative patients are compared in Table 1.

CMR was available in all individuals and revealed right ventricular abnormalities fulfilling the structural criteria for ARVC in all but one case who had a left-dominant form of the disease. Late gadolinium enhancement (LGE) was present in the right ventricular myocardium in 9 cases and in the left ventricle in 11. As presented in Figures 1, 2 and 3, LGE and FDG uptake were present in concordant regions within the ventricular myocardium. In case 1 (Supplementary Figure 2) where there was minimal FDG-uptake, no LGE was seen on CMR.

Genetic studies were available in 11 of the 14 ARVC cases. The details of the identified genetic variants are presented in supplementary table 2. Nine had variants in genes encoding desmosomal proteins, two in LMNA. Two patients (cases 2 and 3) with a left-dominant form of the disease (Figure 3) were carriers of desmoplakin mutations considered likely to be pathogenic. Case 3 also had an additional variant of unknown significance in the LMNA gene. Case 5, who presented with a biventricular form of the disease, was homozygous for a variant in the DSG-2 gene which is predicted to be truncating. No relevant mutations were identified in one patient.

Discussion

This is the first study to evaluate the use of FDG-PET scanning to demonstrate evidence for active myocardial inflammation in patients with ARVC. FDG-PET demonstrated active myocardial inflammation in 36% of patients.

Little is known about the frequency or determinants of myocardial inflammation in patients with ARVC. Inflammatory myocardial infiltrates are reported in up to 80% of cardiac autopsies and explanted hearts [3] and in transgenic mouse models expressing mutations that cause human ARVC [11, 12]. However, the prevalence of inflammation in endomyocardial biopsies from patients with ARVC is much lower [13]. This might be explained by milder disease compared to autopsy and transplant cases or by the patchy and subendocardial distribution of the typical histological lesions seen in classical ARVC.

CMR is a valuable tool in the assessment of patients with ARVC as it provides superior diagnostic accuracy compared to simple two-dimensional echocardiography [14]. CMR also allows for tissue characterization which, though limited in the RV, is useful in identifying patients with left ventricular involvement [15]. More recent CMR mapping techniques (such as T1 and T2 mapping) are of potential use in the evaluation of myocardial inflammation, but to date, no such evidence exists for their utility in ARVC [16].

Nuclear medicine techniques have provided an opportunity to directly image inflammation by visualising the uptake of radiotracers within inflammatory infiltrates [17]. A single study utilising ⁶⁷Ga scintigraphy has reported an increased uptake in the RV free wall in patients with ARVC compared to controls [18]. FDG-PET is an established method for assessing myocardial inflammation and is used increasingly in the clinical work-up of patients with clinically suspected myocarditis [19].

In most of the patients in this study, the indication for an FDG-PET scan was an acute presentation with increasing palpitations and chest pain. It is well recognised that patients with ARVC can develop “hot-phases” characterised by new symptoms, ECG changes and biochemical evidence for myocardial injury [20-22]. In some cases, these phases represent a transition from the subclinical to the overt phase of the disease phenotype [23]. Two studies have demonstrated that these acute presentations are commonly seen with mutations in the

desmoplakin gene [24, 25] and it is noteworthy that 2 of the 5 individuals with a positive FDG-PET scan also carried a pathogenic desmoplakin mutation. Both individuals also had left-dominant cardiac phenotypes. FDG uptake was predominantly seen in the left ventricle and co-existed with LV abnormalities. One exception to this was the case with diffuse LV uptake and focal RV uptake. Little is known about the significance of FDG uptake in the RV. It has been observed in patients with RV failure due to pulmonary hypertension and may reflect metabolic adaptation of myocytes [26].

With the exception of the two biopsies showing histological evidence for sarcoidosis, none of the endomyocardial biopsies revealed inflammatory infiltrates. Sampling error is the most probable explanation for this as the “patchy” distribution of the lesions, as well as their subepicardial localisation, make them difficult to reach through conventional EMB methods [27]. Another important factor is the timing of EMB which was done within a week in only one case. It is also possible that pathological FDG uptake reflects altered myocardial glucose metabolism rather than the presence of inflammatory infiltrates. Pathways specific to adipogenesis such as the peroxisome proliferator-activated receptor signalling pathway are known to be affected in ARVC [28, 29] and it is therefore conceivable that other aspects of metabolism are also affected.

CMR is often used to detect myocardial inflammation, but as we and others have shown, it is not always concordant with findings from FDG-PET imaging [8, 30, 31]. Use of both techniques provides complementary and often incremental information [8]. Due to the small sample size in this study, we were unable to perform a quantitative comparison of FDG uptake and CMR abnormalities, but it is worth noting that in cases imaged with both modalities, the FDG-uptake was more diffuse compared to the distribution of late gadolinium enhancement, yet concordant in terms of the regions affected. This is consistent with previous histological

evidence showing inflammation adjacent to the areas of active myocardial degeneration and fibrofatty replacement [32].

Finally, 2 out of 16 (13%) patients with a definite ARVC diagnosis were diagnosed histologically with cardiac sarcoidosis. This emphasises that cardiac sarcoidosis can ‘mimic’ ARVC and should be considered as a differential diagnosis, especially in non-familial cases [33].

Study Limitations

This study is small and retrospective but has demonstrated that some patients with ARVC have features consistent with active myocardial inflammation. The majority of the patients included in this study were symptomatic and therefore there is some selection bias among this cohort. CMR T1 and T2 mapping techniques were unavailable in most cases and were of low quality in the rest. It is well known that endomyocardial biopsy can be negative in patients with cardiac sarcoidosis due to sampling error, however the presence of FDG uptake in genetically determined ARVC cases supports our hypothesis that myocarditis is an intrinsic feature of ARVC. Future studies using a systematic approach to imaging, genetic testing and cardiac biopsy is imperative to better understand the role of FDG-PET and CMR in the characterization of myocardial inflammatory substrate in patients with ARVC.

Conclusions

This is the first study to provide an *in vivo* affirmation that patients with symptomatic ARVC have abnormal FDG-PET scans consistent active myocardial inflammation. FDG-PET imaging is a potentially useful tool in the work-up for patients with ARVC and increasing symptoms or arrhythmia.

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Table 1: Clinical Characteristics of the study population*

Clinical Characteristics	Overall (n=14)	Positive ¹⁸ F-FDG PET	Negative ¹⁸ F-FDG PET	P-value
		(n=5)	(n=9)	
Sex (Male)	10 (71)	3 (60)	7(78)	0.58
Age (years)	41.7±13.8	49.4±8.6	37.4±14.7	0.16
Epsilon waves	0(0)	0(0)	0(0)	1.0
RBBB	1(7)	0(0)	1(11)	1.0
History of Sustained VT	6 (43)	1 (20)	5 (56)	0.30
RVOTd (mm)	36.3±5.2	34.0±3.8	37.5±5.6	0.39
RVWMA	13(93)	4 (80)	9(100)	0.36
RV-LGE	9 (64%)	3 (60%)	6 (67%)	1.0
LVEF (%)	53.4±9.1	48.4±11.1	56.1±7.1	0.23
LVEDD (mm)	52.0±5.7	52.3±5.2	51.5±7.3	0.71
LVWMA	8 (57)	5(100)	3 (33)	0.03
LV-LGE	11 (79)	5 (100%)	6 (75%)	0.49
Elevated Troponin T on presentation	3 (21)	1 (20)	2 (22)	1.0

Frequencies for categorical variables are reported as n(%) and continuous variables' values as mean±SD. FDG=Fluorodeoxyglucose; LGE=late gadolinium enhancement; LVEF=Left ventricular ejection fraction; LVWMA=Left ventricular wall motion abnormalities; PET=Positron emission tomography; RBBB=Right bundle branch block; RVOTd=Right ventricular outflow tract diameter; RVWMA=Right ventricular wall motion abnormalities; TWI=T-wave inversions; VT=ventricular tachycardia. *Excluding the 2 patients that were diagnosed with sarcoidosis.

Figure 1 Case presentation of patient with diffuse LV FDG uptake and significant right ventricular FDG uptake

A 53-year-old man (Case 4) presented with atypical chest pain and was found to have T-wave inversion in the precordial leads. There was no family history of cardiomyopathy or sudden cardiac death. Coronary angiography demonstrated only minor atheroma. Troponin-T on presentation was within normal limits. Cardiac MRI revealed mild right ventricular dilatation (EDVi 91 ml/m²) with dyskinesia in the inferior wall, and apex. LV was normal in size but had a borderline low EF. LGE was present in both ventricles (white arrows). FDG-PET showed homogeneous increased uptake in the LV myocardium suggestive of failure to suppress physiological uptake however focal increased uptake was seen throughout the RV wall (white arrows) suggesting abnormal myocardial metabolism within the RV. Genetic analysis was negative. RV endomyocardial biopsy showed fibrofatty replacement of the myocardium consistent with ARVC. Myocytes appeared hypertrophied with large irregular nuclei. No inflammatory infiltrates were identified.

Figure 2 Case presentation of patient with a DSG-2 variant and biventricular ARVC

A 36-year-old man (Case 5) presented with atypical chest pain and was found to have T-wave inversion on his baseline ECG. There was no family history of cardiomyopathy or sudden cardiac death. Troponin-T on presentation was within normal limits. 24h Holter monitoring identified 556 ventricular ectopics. Cardiac MRI showed normal LV dimensions with mildly impaired LV systolic function and multiple hypokinetic areas. RV appeared dilated with impaired systolic function and multiple regional wall motion abnormalities. There was patchy late gadolinium enhancement in the anteroseptal, anterior and anterolateral regions of the LV wall (white arrows). There was concordant focal FDG uptake (white arrows). Myocardial

fibrosis in the absence of inflammatory infiltrates was observed in the EMB. Genetic testing revealed homozygosity for a truncating variant in DSG-2.

Figure 3 Case presentation of two patients with left dominant ARVC, carriers of desmoplakin mutations

A: 52-year-old female (Case 3) presented with chest pain and palpitations. She had a history of palpitations since the age of 16 years and a family history of sudden cardiac death in her brother aged 27. She had an elevated Troponin T with unobstructed coronary arteries on angiography. She was referred for further cardiomyopathy evaluation. Her 6-month follow-up is presented in this figure. Genetic testing identified mutations in the DSP and Lamin A/C genes. A 12 lead ECG demonstrated low voltages and inferolateral T-wave inversion. 24h Holter monitoring revealed 774 ventricular ectopics. Cardiac MRI showed normal biventricular dimensions, but hypokinesia of the LV lateral wall and there were RV free wall motion abnormalities. Subepicardial LGE was seen in the mid anterior wall and anteroseptum and basal inferolateral wall (white arrows). FDG-PET revealed concordant FDG uptake in the areas where LGE was present (white arrows). Myocardial fibrosis in the absence of inflammatory infiltrates was observed in the EMB.

B: 59-year-old lady (Case 2) presented with palpitations, chest pain and a broad-complex tachycardia with LBBB morphology which reverted to sinus rhythm spontaneously. She described a history of intermittent chest pain and palpitations over the previous year. Multiple polymorphic ventricular ectopics and episodes of non-sustained VT were noted. Her ECG showed lateral T-wave inversion and marginally prolonged terminal activation duration in lead V2 (60 ms). Her Troponin T levels were within normal limits and angiogram showed unobstructed coronaries. Cardiac magnetic resonance demonstrated moderate LV dilatation

with an LVEF of 37% and dyskinesia of the mid-inferior wall. Her RV was non-dilated and without regional wall-motion abnormalities. Epicardial LGE was noted in the inferolateral wall (white arrows). An FDG-PET scan revealed increased FDG uptake in the areas of LGE on cardiac MRI but also in the mid-intraventricular septum. Genetic analysis identified a heterozygous a mutation in the DSP gene.

C: Haematoxylin and eosin staining of the LV endomyocardial biopsy obtained from Case 3 showing extensive fibrosis. No inflammatory infiltrates were identified.

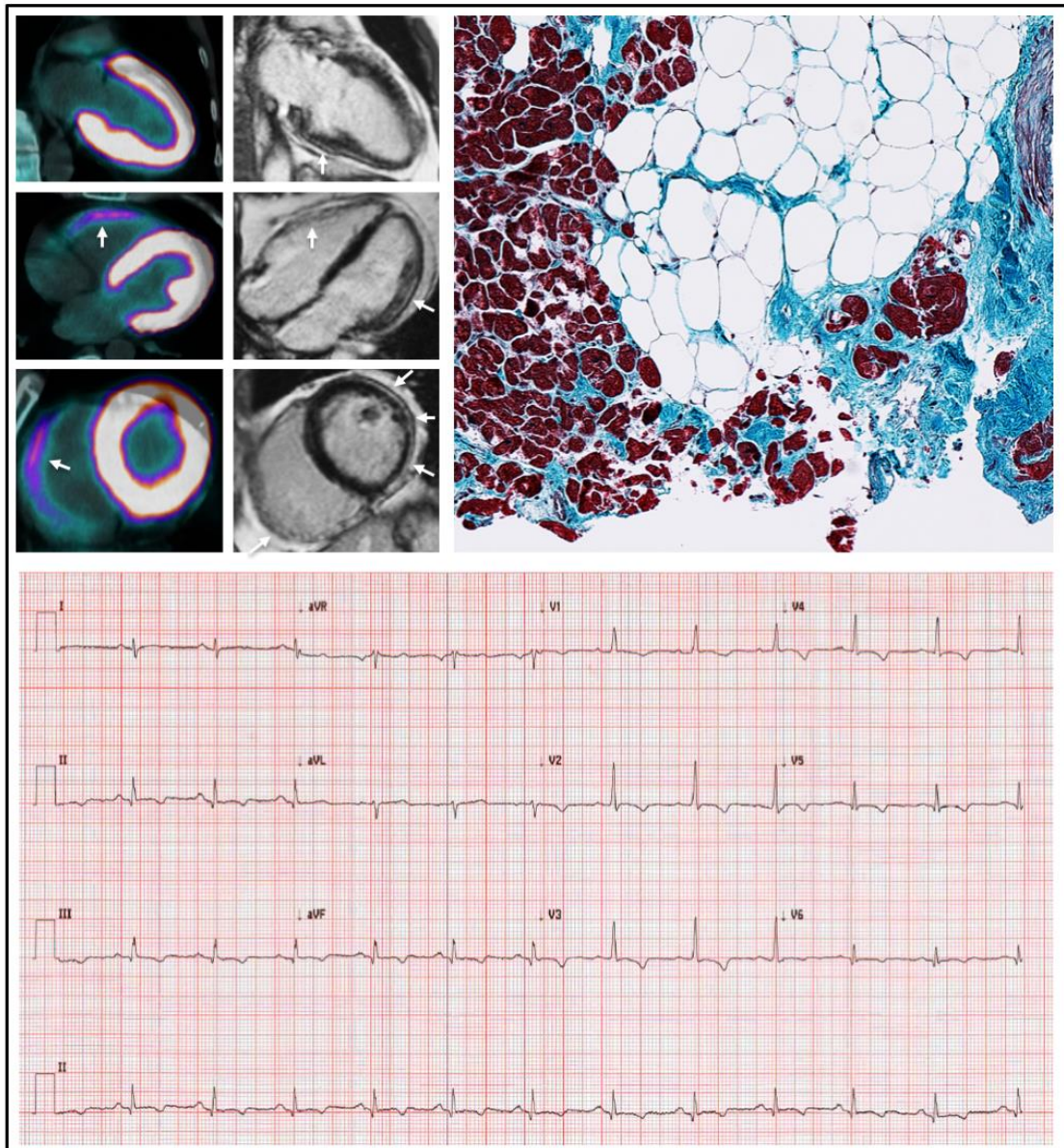


Figure 1



Figure 2

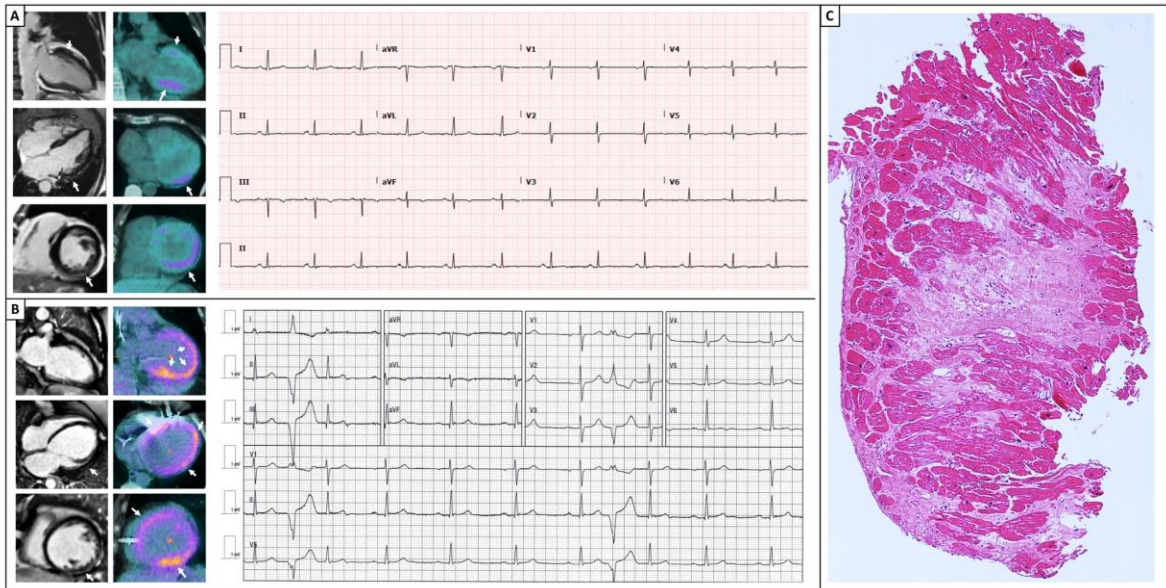
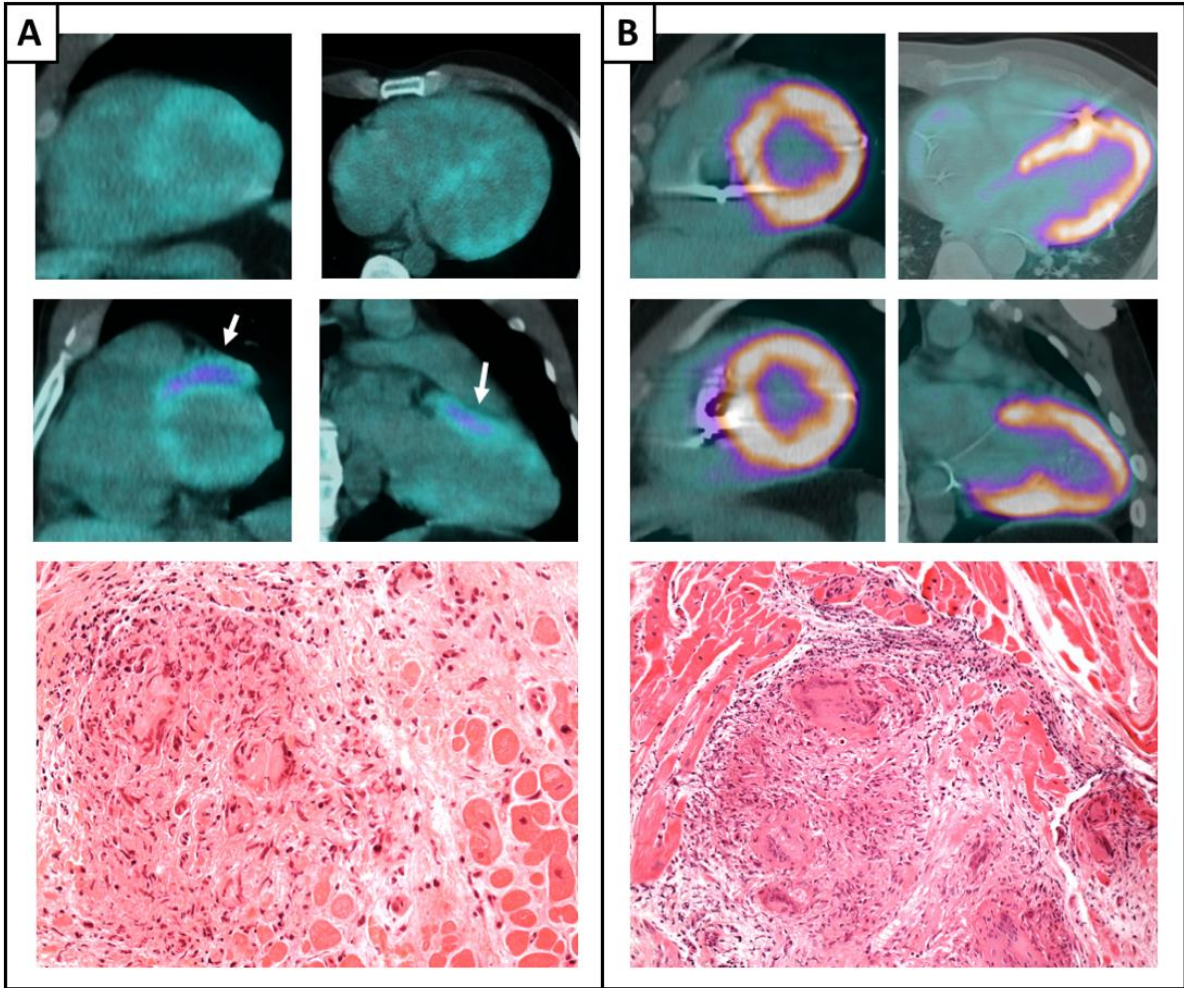
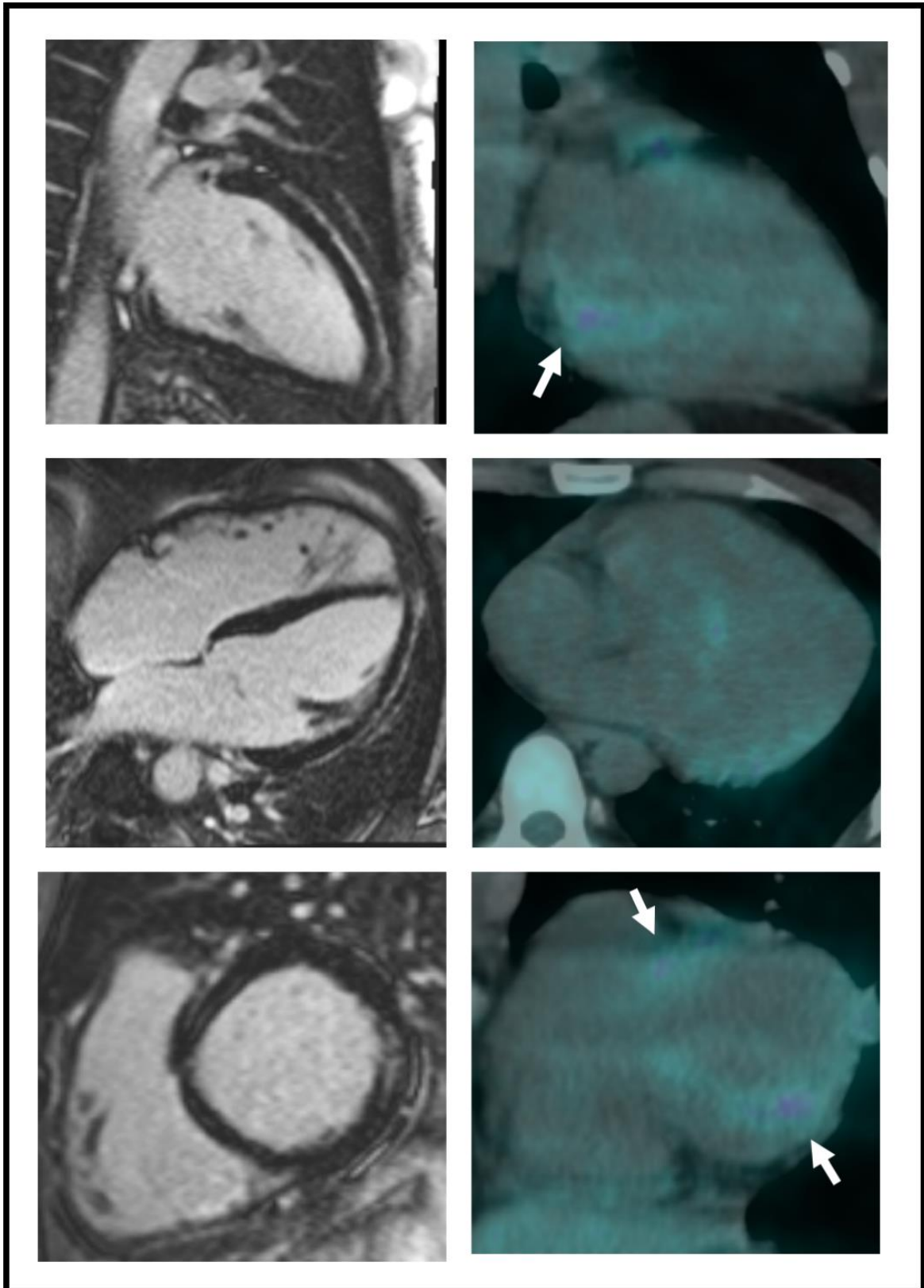


Figure 3



Supplementary Figure 1



Supplementary Figure 2