Circulation: Cardiovascular Imaging

CARDIOVASCULAR IMAGES

^{68}Ga-Dotatate Hybrid Positron Emission Tomography/Magnetic Resonance Imaging for Noninvasive Early Detection of Heart Transplant Rejection

Ana Devesa, MD, PhD; Philip M. Robson, PhD; Renata Pyzik, BS; Adam Jacobi, MD; Munir Ghesani, MD; Anelechi Anyanwu, MD; Donna Mancini, MD; Zahi A. Fayad, PhD; Maria Giovanna Trivieri, MD, PhD

Endomyocardial biopsy (EMB) is the gold standard for diagnosing heart transplant rejection, but it is limited by sampling error and has associated morbidity. Cardiac magnetic resonance and 18F-fluorodeoxyglucose-positron emission tomography (PET) have been introduced as a complementary approach to EMB in the detection of cardiac allograft rejection; ^{18}F-fluorodeoxyglucose specificity, however, is limited by the uptake of normal myocardium and requires specific patient preparation, with failure of adequate myocardial suppression potentially leading to ambiguous results.[1] ^{68}Ga-Dotatate, a somatostatin receptor type 2-binding radiotracer, has emerged as an alternative to ^{18}F-fluorodeoxyglucose for the evaluation of cardiovascular inflammation due to its specific binding to inflammatory cells.[2] In addition, somatostatin receptor imaging has shown promising results in the early identification of acute allograft rejection in a rat model using PET[3] and for rejection prediction in human using single-photon emission computed tomography.[4] Because PET imaging has higher effective resolution and sensitivity compared with single-photon emission computed tomography, it might improve rejection prediction further. On this basis, we aimed to evaluate whether cardiac ^{68}Ga-Dotatate uptake could be a marker of rejection in transplant patients, especially for biopsy-negative cases where rejection is clinically suspected. The study was approved by the Institutional Review Board (HS-17-00371). Imaging protocols are included in the Supplemental Material.

^{68}Ga-Dotatate-PET/magnetic resonance (MR) was performed in 4 heart transplant patients, 3 with suspected acute allograft rejection presenting with acute heart failure, and 1 control (Table S1). Patient 1 was admitted for acute heart failure; EMB showed grade 3R (International Society for Heart and Lung Transplantation) acute cellular rejection (ACR) with associated antibody-mediated rejection grade 1. She was treated with high-dose steroids and cytolytic agents in accordance with local protocols. Subsequent EMB showed no antibody-mediated rejection and ACR(1R). She again presented 10 days later, with evidence of 2:1 atrioventricular block. A ^{68}Ga-Dotatate-PET/MR showed intense uptake in the basal anteroseptum, consistent with the observed conduction abnormality (Figure 1A). Blinded biopsy of the right ventricle septum was read as ACR0 and antibody-mediated rejection grade 1, while an imaging-guided EMB (4 days after PET/MR) showed significant mononuclear cell infiltrates in specimens obtained from the basal septum, correlating with the area of ^{68}Ga-Dotatate uptake (ACR-1R and antibody-mediated rejection grade 1). Average standardized uptake value (SUV_{mean}, 0.64±0.13) and target-to-background ratio (TBR_{mean}, 1.4±0.3) were higher than the control (SUV_{mean}, 0.62±0.06; TBR_{mean}, 1.1±0.1). Notably, T2 values on cardiac magnetic resonance were similarly increased in the basal anteroseptum, colocalizing with ^{68}Ga-Dotatate uptake, but average T2 values were normal. Patient 2 was admitted for acute heart failure

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Correspondence to: Maria Giovanna Trivieri, MD, PhD, One Gustave L. Levy Place, Box 1030, New York, NY 10029-6574. Email Mariagiovanna.trivieri@mountsinai.org
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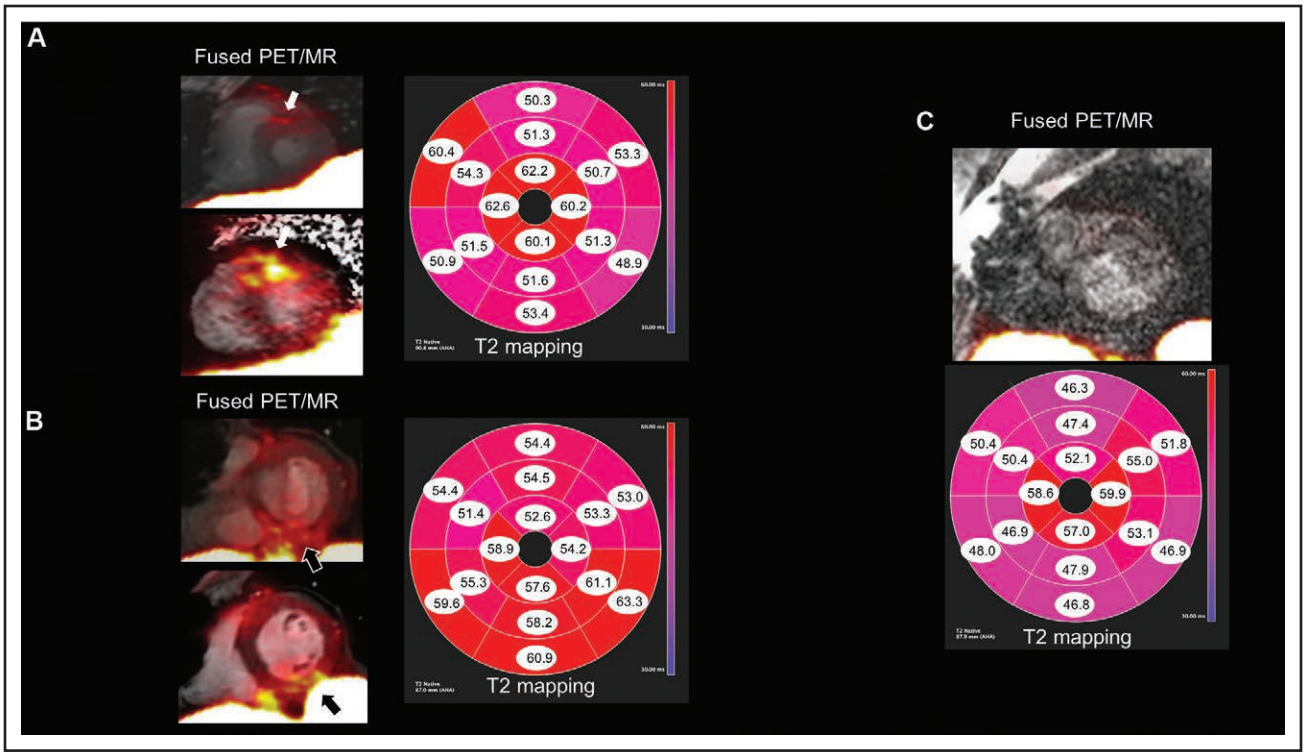

Figure 1. ^{68}Ga-Dotatate-positron emission tomography (PET)/magnetic resonance (MR) imaging in rejection patients vs control. Representative examples of ^{68}Ga-Dotatate-PET/MR imaging in heart transplant patients with (**A** and **B**) and without rejection (control, **C**). Panels show fused PET/MR imaging, and T2 mapping polar map is represented for each patient (T2 values are represented in milliseconds; reference values for T2 mapping are detailed in Supplemental Material). **A**, This shows ^{68}Ga-Dotatate uptake in the basal anteroseptum in a patient with allograft rejection (**arrows**), colocalizing with an increased T2 time in basal anteroseptum, but with normal average T2 values; (**B**) shows ^{68}Ga-Dotatate uptake in the inferior wall (**arrows**), colocalizing with abnormal T2 values, in a patient with allograft rejection; (**C**) shows the absence of ^{68}Ga-Dotatate uptake in a patient with a heart transplant and no signs of rejection. Please note abnormal T2 values in mid anterolateral wall and apical segments.

with EMB showing ACR(1R). After completing treatment for rejection, he underwent ^{68}Ga-Dotatate-PET/MR and EMB; both the scan and EMB were negative, which was concordant with his clinical improvement. Six weeks later, he had recurrent acute heart failure symptoms and elevated troponin. A second ^{68}Ga-Dotatate-PET/MR revealed uptake in the left lateral wall and interatrial septum up to the atrioventricular junction (Figure 2). Following the scan, he developed atrioventricular block, which was consistent with the area of inflammation detected by ^{68}Ga-Dotatate. Notably, a conventional EMB of the interventricular septum, performed the same day as the PET/MR, was negative. SUV_{mean} and TBR_{mean} were higher in the first scan (visually negative) compared with control (SUV_{mean}, 1.16±0.10 versus 0.62±0.06; TBR_{mean}, 1.3±0.1 versus 1.1±0.1) but lower than in the second scan (visually positive; SUV_{mean}, 1.20±0.05; TBR_{mean}, 1.7±0.1). Concordantly, T2 values were higher in the second than in the first scan; however, they were diffusely increased, without localizing to a specific region of the myocardium. Patient 3 received treatment for ACR(3R), and a negative biopsy was obtained after completion of treatment. Three weeks later, a ^{68}Ga-Dotatate-PET/MR was performed, showing focal uptake in the basal inferior wall. SUV_{mean} and TBR_{mean} were higher than the control (SUV_{mean}, 1.48±0.13 versus 0.62±0.06; TBR_{mean}, 1.5±0.1 versus 1.1±0.1; Figure 1B). A subsequent EMB (17 days later) was positive for ACR(2R). Increased T2 values in the inferior wall correlated with ^{68}Ga-Dotatate findings. Coronary angiography did not show significant cardiac allograft vasculopathy in any of the patients. Patient 4 (control), asymptomatic, underwent a routine EMB with no signs of rejection. ^{68}Ga-Dotatate-PET/MR (6 days later) showed no uptake; however, abnormal T2 values were found in anterolateral and apical segments (Figure 1C).

These data support the hypotheses that (1) acute allograft rejection can be identified by ^{68}Ga-Dotatate-PET/MR, (2) the use of this technique surpasses some of the limitations of EMB, and (3) this hybrid technique is superior to cardiac magnetic resonance alone.

All the patients with suspected rejection exhibited positive ^{68}Ga-Dotatate-PET/MR scans. The presence and location of ^{68}Ga-Dotatate uptake correlated well with clinical events such as conduction abnormalities. Furthermore, ^{68}Ga-Dotatate-PET/MR overcomes a key limitation of EMB by identifying affected areas inaccessible to biopsy. This technique could help increase the diagnostic yield of EMB by identifying areas of inflammation and guiding

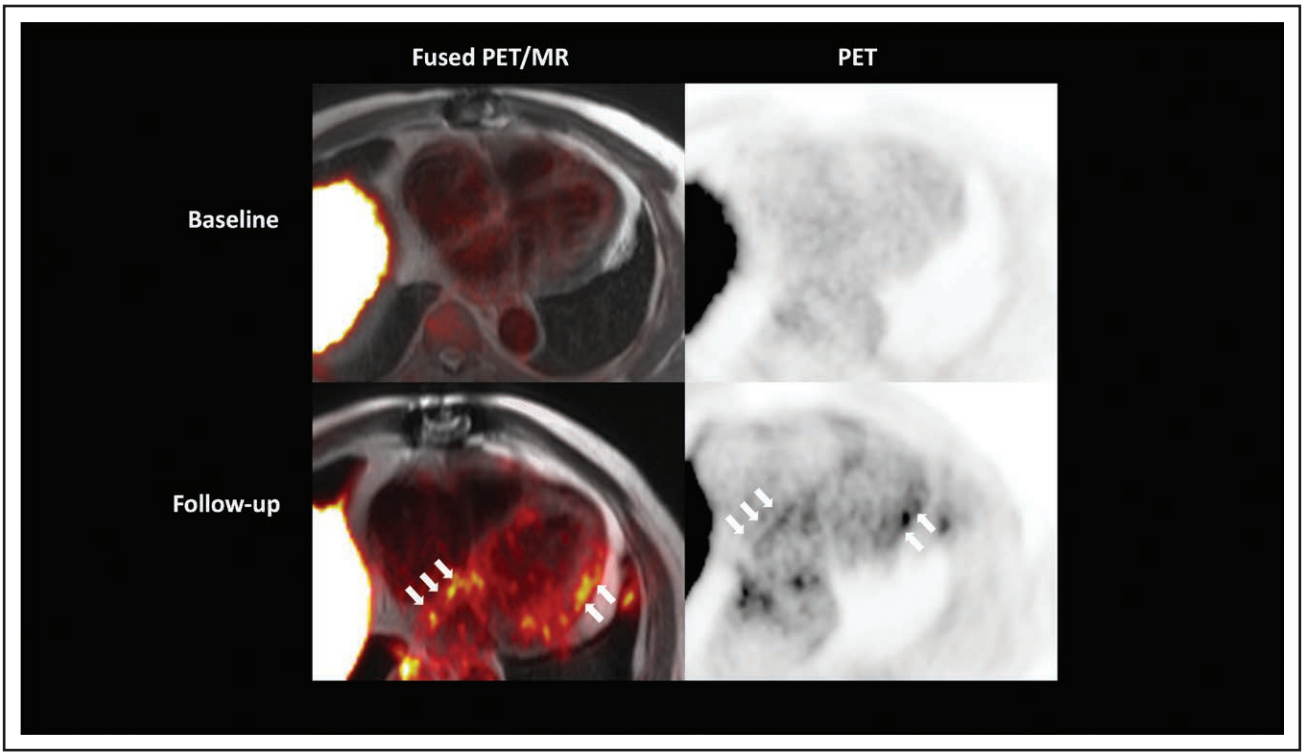

Figure 2. Positive ^{68}Ga-Dotatate-positron emission tomography (PET)/magnetic resonance (MR) imaging in a biopsy-negative rejection patient.

Representative examples of fused ^{68}Ga-Dotatate-PET/MR imaging. The baseline scan was performed after completing treatment for rejection and showed no evident visual ^{68}Ga-Dotatate uptake. The recurrence of heart failure symptoms after 6 weeks led to a follow-up PET/MR (follow-up scan), which showed increased ^{68}Ga-Dotatate uptake in the interatrial septum reaching for the atrioventricular junction and in the left lateral ventricular wall (**arrows**). This patient subsequently developed a complete heart block, likely secondary to the involvement of the atrioventricular junction.

subsequent biopsy sampling. Lastly, ^{68}Ga-Dotatate-PET/MR can aid in the early identification of rejection in biopsy-negative patients, thus allowing prompt treatment initiation, supporting the diagnosis when histologic findings are equivocal and avoiding multiple biopsies.

PET/MR appears superior to stand-alone cardiac magnetic resonance, although rigorous evaluation was limited in this case series. Increased T2 values, a marker of inflammation/edema, have been described in ACR,[1] but with only moderate positive predictive value and limited utility in the early posttransplant stages. In contrast, ^{68}Ga-Dotatate-PET/MR, with its ability to detect inflammatory cells directly, accurately identified allograft rejection across a range of durations after transplant (0–13 years). Average T2 values were normal in a patient with rejection, while ^{68}Ga-Dotatate-PET/MR was positive. Conversely, T2 values were abnormally increased in the control with a negative ^{68}Ga-Dotatate scan, implying a low specificity of these parameters in identifying rejection. Regional distribution of the increased T2 values might also not be specific enough to allow image-guided biopsy. Lastly, ^{68}Ga-Dotatate-PET/MR does not require gadolinium-based contrast.

SUV_{mean} and TBR_{mean} were higher in the rejection group than in the control, even when visual ^{68}Ga-Dotatate uptake was absent. These values may represent low-grade inflammation that contributes to diffuse myocardial edema, as they correlated well with mean T2 values (Pearson coefficient=0.55 and 0.93), as opposed to SUV_{max} and TBR_{max}, which seem to identify focal inflammation.

In conclusion, our data support the use of ^{68}Ga-Dotatate-PET/MR imaging as a noninvasive and complementary alternative to EMB in the detection of heart transplant rejection. The use of this technique for the diagnosis and prognosis of acute allograft rejection warrants further investigation.

ARTICLE INFORMATION

Affiliations

BioMedical Engineering and Imaging Institute, Icahn School of Medicine at Mount Sinai, New York, NY (AD, PMR, RP, ZAF, MGT). Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain (AD). Zena and Michael A. Weiner Cardiovascular Institute (AD, DM, MGT), Department of Radiology (AJ), Division of Nuclear Medicine (MG), and Department of Cardiovascular Surgery (AA), Icahn School of Medicine at Mount Sinai, New York, NY.

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Disclosures

None.

Supplemental Material

Supplemental Methods
Table S1

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