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Myocardial perfusion reserve and global longitudinal strain as potential markers of coronary allograft vasculopathy in late-stage orthotopic heart transplantation

Akhil Narang¹, John E. Blair¹, Mita B. Patel², Victor Mor-Avi¹, Savitri E. Fedson³, Nir Uriel¹, Roberto M. Lang^{1,4}, and Amit R. Patel^{1,4}

¹Department of Medicine, University of Chicago Medicine, 5758 S. Maryland Avenue, MC9067, Chicago, IL 60637, USA

²Department of Medicine, Medical College of Wisconsin, Milwaukee, WI, USA

³Center for Medical Ethics and Health Policy, Baylor School of Medicine, Houston, TX, USA

⁴Department of Radiology, University of Chicago, Chicago, IL, USA

Abstract

Coronary allograft vasculopathy (CAV) is a major cause of mortality in late-stage orthotopic heart transplantation (OHT) patients. Recent evidence has shown that myocardial perfusion reserve (MPR) derived from vasodilator cardiovascular magnetic resonance imaging (vCMR) and global longitudinal strain (GLS) from transthoracic echocardiography (TTE) are useful to detect CAV. However, previous studies have not comprehensively addressed whether these parameters are confounded by allograft rejection, myocardial scar/fibrosis, or allograft dysfunction. Our aim was to determine whether changes in late post-OHT MPR and GLS are due to CAV or other confounding factors. Twenty OHT patients (time from transplant to vCMR was 8.1 ± 4.1 years) and 30 controls (10 healthy volunteers and 20 with prior myocardial infarction to provide perspective with regards to the severity of any abnormalities seen in post-OHT patients) underwent vasodilator vCMR from which MPR index (MPR_i), left ventricular ejection fraction (LVEF), and burden of late gadolinium enhancement (LGE) were quantified. TTE was used to measure GLS. The presence of CAV was determined from invasive coronary angiograms using thrombolysis in myocardial infarction (TIMI) frame counts and grading severity per guidelines. Previous endomyocardial biopsies were reviewed to assess association with episodes of rejection. We examined the correlations between MPR_i and GLS with markers of CAV, allograft function, scar/fibrosis, and rejection. MPR_i was abnormal in post-OHT patients compared to both healthy volunteers and MI controls. While there was no relationship between MPR_i or GLS and LVEF, episodes of rejection, or LGE burden, both MPR_i and GLS were associated with TIMI frame counts and presence and severity of CAV. Additionally, MPR_i correlated with GLS ($R = 0.68$, $P = 0.0002$). In conclusion, MPR_i and GLS are abnormal in late-stage OHT and associated with CAV, but not related to allograft rejection, myocardial scar/fibrosis, or allograft dysfunction. Non-invasive monitoring of MPR_i and GLS may be a useful strategy to detect CAV.

Compliance with ethical standards

Conflict of interest: There are no conflicts of interest among the authors.

Keywords

Magnetic resonance imaging; Heart transplantation; Allograft vasculopathy; Myocardial perfusion; Longitudinal strain; Echocardiography

Introduction

Orthotopic heart transplantation (OHT) is an important treatment for patients with end-stage, refractory heart failure. Advances in immunosuppressive therapies have resulted over time in improved longevity of post-OHT recipients [1]. Presently, the leading causes of cardiovascular mortality in late post-OHT (> 10 years) patients include graft failure and coronary allograft vasculopathy (CAV) [2]. The diagnosis of CAV is typically confirmed with invasive coronary angiography, often with intravascular ultrasound (IVUS) to detect abnormal intimal thickening. Other invasive markers of CAV include abnormal coronary flow reserve or TIMI frame counts [3, 4]. Lately however, there is a growing interest to identify a robust, non-invasive technique to diagnose and monitor CAV.

Prior investigations with non-invasive modalities [vasodilator cardiovascular magnetic resonance (vCMR), myocardial contrast echocardiography, single-photon emission computed tomography (SPECT), and positron emission tomography (PET)] have reported conflicting results on how myocardial perfusion reserve (MPR) changes in the post-OHT patient with some suggesting no change and others suggesting a decrease over time [5–12]. More recent studies have shown that MPR derived from vCMR imaging is a promising tool to diagnose CAV when compared to invasive coronary angiography with IVUS [13]. In the transplanted heart with CAV, the capacity for coronary arteries and microcirculation to dilate is impaired, resulting in abnormal MPR [14]. However previous studies, especially in late post-OHT period, have not adequately addressed whether other variables such as allograft rejection, myocardial scar/fibrosis, or allograft dysfunction are possible confounders responsible for reduced MPR.

Similar to reduced MPR by vCMR, abnormal global longitudinal strain (GLS) derived from transthoracic echocardiography (TTE) has been recently shown to be associated with CAV and coronary microvascular dysfunction [15–17] in studies from a single group of investigators. Moreover, the same group has reported that decreased GLS is associated with repeated episodes of allograft rejection [18]. However, it remains unknown whether GLS is similarly confounded by allograft rejection or myocardial scar/fibrosis. It is also not well known to what extent GLS and MPR are related.

Neither vCMR-derived MPR nor TTE-derived GLS have been adopted in routine clinical practice in the context of post-OHT CAV evaluation, thus highlighting the need to better understand both tools. Compared to invasive coronary angiography, a reliable non-invasive approach to CAV would be of great value. Specific advantages of vCMR include the ability to quantify myocardial perfusion and microvascular function [19–21], while TTE is nearly universal and could easily be used in this patient population. Accordingly, the aim of this study was to determine whether MPR and GLS are associated with markers of CAV and to

what extent they are affected by other confounders (allograft rejection, myocardial scar/fibrosis, or allograft dysfunction), as well as whether they are associated with each other.

Methods

Population and study design

The study included 20 consecutive patients post-OHT (at least 1 year after transplant; mean 8.1 ± 4.1 years), who underwent vCMR, echocardiogram, and coronary angiogram over a period of 2 years and also had complete records of endomyocardial biopsies available. We used two different control groups who all underwent vCMR: 20 patients with a previous history of documented myocardial infarction (MI), confirmed by invasive coronary angiogram, who were successfully revascularized, and 10 healthy volunteers with no history of cardiovascular disease. The control groups did not undergo echocardiogram. The MI control group was included to provide perspective with regards to the severity of any abnormalities seen in post-OHT patients in the context of a well-described cardiovascular disorder. All subjects were selected from a registry of studies performed at a single academic teaching hospital. The Institutional Review Board at the University of Chicago approved the study.

In order to determine the factors that govern changes in MPR and GLS, OHT patients were also required to have had:

1. vCMR examination, the results of which were used to determine MPR and presence of myocardial scar/fibrosis;
2. transthoracic echocardiography (TTE) examination, the results of which were used to determine GLS.
3. invasive coronary angiography, the results of which were used to detect CAV;
4. complete record of post-OHT endomyocardial biopsies to determine the relationship between rejection and MPR or GLS.

In order to understand the factors responsible for the changes in MPR and GLS, we employed a multiparametric strategy. To this effect, vCMR was used to determine whether scar/fibrosis is related to MPR or GLS, endomyocardial biopsies were examined to evaluate whether rejection is related to MPR or GLS, and coronary angiograms were analyzed to examine the relationship between markers of CAV and MPR or GLS.

vCMR protocol

Each subject underwent a vCMR study, after clinical evaluation, in which baseline demographics, current symptoms, past medical history, exercise capacity, and current medications were assessed. Patients were excluded if they had an implantable cardioverter-defibrillator, pacemaker or other standard contraindications to gadolinium-enhanced vCMR, such as claustrophobia, severe reactive airway disease, high-grade atrioventricular (AV) nodal block, or $GFR < 30 \text{ ml/min/1.73 m}^2$. A 12-lead electrocardiogram was performed in all patients prior to vCMR imaging to rule out high-degree AV nodal block. Patients were asked to stop all nitrates and caffeine-containing products 12 h before the vCMR exam.

Each vCMR study was performed using a 1.5-T MRI scanner (Achieva, Philips, Best, Netherlands) and a 5-element phased array cardiac coil. Retrospectively gated cine-CMR images were obtained using a steady-state free precession (SSFP) pulse sequence (temporal resolution ~ 40 ms). Standard long-axis views, including four-chamber, two-chamber, and three-chamber, were obtained. In addition, one series of short-axis slices (6 mm thickness, 4 mm gap) spanning from left ventricular (LV) base to apex was acquired. Myocardial perfusion imaging was performed during vasodilator stress using a hybrid gradient echo/echo planar imaging sequence (voxel size ~ 2.5 × 2.5 mm, slice thickness 10 mm, flip angle 20°, delay time 80 ms, and SENSE factor 1.3). Images of three LV short-axis slices were acquired during first pass of gadolinium-contrast agent (Omniscan™ or MultiHance™, 0.05–0.1 mmol/kg, depending on GFR, injected at 4 ml/s, IV) 1 min after regadenoson administration (Lexiscan 0.4 mg IV bolus, Astellas Pharma, Deerfield, IL) and then again during recovery, 15 min after the administration of aminophylline (75 mg IV). Late gadolinium enhancement (LGE) images of the same cine-CMR short- and long-axis views were obtained 5 min after the second infusion of contrast, using a T1-weighted gradient echo pulse sequence with a phase sensitive inversion recovery reconstruction (TR 4.5 ms, TE 2.2 ms, TI 250–300 ms, flip angle 30°, flip angle 5°, voxel size 2 × 2 × 10 mm, SENSE factor 2, no gap). A Look-Locker sequence was used to select an inversion time between 200 and 250 ms for optimal nulling of normal myocardium. Heart rate (HR) was monitored continuously, and blood pressure (BP) was recorded at rest, hyperemia, and during recovery.

vCMR image analysis

Cine perfusion and LGE vCMR images were analyzed using commercial software (Medis, Leiden, Netherlands). Short-axis slices were used to measure left and right ventricular end-diastolic (first phase of the R-wave triggered acquisition) and end-systolic (the phase with the smallest ventricular cavity area in the majority of slices) volumes, LV mass, and left and right ventricular ejection fraction using the Simpson method of disks [22]. All volumes and masses were indexed for body surface area. Detection of regional wall motion abnormalities was primarily based on the short-axis view and confirmed in orthogonal long-axis views. The burden of LGE was quantified using commercially available software (Medis, Leiden, Netherlands) using the full-width, half-maximum (FWHM) technique and was expressed as a fraction (%) of LV mass [23].

Time-intensity curves generated from stress and recovery perfusion images were used to determine myocardial perfusion reserve (MPR), which was calculated as the upslope ratio of stress to recovery (Fig. 1). Myocardial perfusion reserve index (MPRi) was determined by normalizing MPR to the LV cavity upslope to account for differences in contrast volume and cardiac output during different imaging conditions [24]. Due to denervation of the transplanted heart and the potential for differences in HR and BP between the post-OHT patients and controls after administration of regadenoson, MPRi was also normalized to the rate-pressure-product measured during stress [25]. The equation used to determine MPRi was:

$$MPRi = \frac{\left(\text{Upslope}_{Myocardium} \middle| \text{Upslope}_{LV cavity} \right)_{Stress}}{\left(\text{Upslope}_{Myocardium} \middle| \text{Upslope}_{LV cavity} \right)_{Rest}} \times 10^3 \times (\text{rate pressure product})_{stress}$$

MPRi was determined for the post-OHT patients and the healthy controls by tracing an entire myocardium in the mid-left ventricular myocardial slice (global perfusion). For the MI controls, MPRi was assessed in a segment remote to any ischemic or infarcted territory, based on LGE and invasive coronary angiography.

Echocardiography

Comprehensive two-dimensional TTE was performed using an iE33 imaging system (Phillips Healthcare, Andover, MA) with either an S5 or X5 transducer. Frame rate was maximized by increasing the depth and decreasing the sector width. The focal point was optimized for the midventricular level of the apical views. Left ventricular ejection fraction (LVEF) was quantified using the biplane method of discs (modified Simpson's rule) in the apical two- and four-chamber views [26]. The TTE dataset closest to the vCMR was analyzed. Strain analysis was performed using QLAB 10 (Phillips Healthcare, Andover, MA). Endocardial contours were manually corrected to optimize tracking throughout the cardiac cycle, and segments with inadequate tissue tracking were excluded from analysis. Longitudinal strain was measured in apical two-, three-, and four-chamber views and then averaged to obtain GLS.

Invasive coronary angiography

As part of routine surveillance for CAV, all patients underwent regularly scheduled invasive coronary angiograms (time from coronary angiogram to vCMR = 6 months in 30% of patients). Using either a radial or femoral arterial approach, standard catheters were used to access the left and right coronary systems. Injection of contrast during cine fluoroscopy was performed in multiple orthogonal views and recorded at a frame rate of either 15 or 30 frames per second. The coronary angiogram most proximal in time to the vCMR study was reviewed by an experienced interventional cardiologist (JEB) blinded to all other clinical variables. CAV was graded according to standardized International Society of Heart and Lung Transplantation (ISHLT) criteria [27] as none (CAV 0), mild (CAV 1), moderate (CAV 2), or severe (CAV 3).

TIMI frame count analysis was also performed by an experienced interventional cardiologist (JEB) who was blinded to all other study variables, using methodology outlined previously [28]. The number of cine frames required for contrast to reach the distal bifurcation of the left anterior descending artery (LAD) was determined using Centricity Cardio Enterprise (GE Healthcare, Milwaukee, WI). For cineangiograms recorded at 15 frames/s, the calculated TIMI frame count was multiplied by 2.

Endomyocardial biopsy and rejection analysis

Surveillance endomyocardial biopsies were routinely performed in post-OHT patients. Using fluoroscopic guidance, a biptome was advanced into the right ventricle where 3–4

biopsy specimens of the septum were obtained for pathologic analysis to assess cellular or humoral rejection. Cellular rejection was reported per the 1990 standardized grading method set forth by the ISHLT [29]. The severity of rejection was classified as none (Grade 0), mild (Grades 1A or 1B), moderate (Grades 2 or 3A), or severe (Grades 3B or 4). The absolute number of cellular rejection episodes was determined by counting all rejection episodes noted on endomyocardial biopsy. Additionally, humoral rejection was assessed on each endomyocardial biopsy by the presence or absence of C4d staining.

Statistical analysis

Categorical variables were expressed as percentages and continuous variables as mean \pm SD or medians with first and third quartiles. One-way ANOVA analysis was used to test the differences in vCMR characteristics while Student's unpaired *t* test was used to test the significance of the difference between the individual groups when necessary. The differences in MPRi between post-OHT, normal controls, and MI controls were tested using a Mann Whitney test. The median, first, and third quartile were used to create Whisker plots of MPRi. Analysis of rejection, CAV, and allograft function was carried out using linear regression analysis (Microsoft Excel 2011) and/or a Student's unpaired *t* test (STATA 12, College Station, TX, USA). A P-value of < 0.05 was considered statistically significant. Multivariable regression analysis was used to evaluate the relationship between MPRi or GLS and TIMI frame counts adjusted for time from transplant to vCMR.

Results

Patient demographics and CMR characteristics

Demographic data is shown in Table 1. As expected, both the post-OHT group and the MI controls had multiple known risk factors associated with coronary disease, compared to the normal control group. Baseline vCMR characteristics are shown in Table 2. As expected, the OHT group had similar LVEF compared to normal controls, but elevated LV mass index. Similarly, MI controls had elevated LV mass index but also reduced LVEF.

Hemodynamics response and myocardial perfusion reserve

During hyperemia and recovery, there were no major differences among the study groups in the hemodynamic response (Fig. 2). The BP at baseline of the post-OHT, normal, and MI groups was 133/83 ($\pm 13/9$), 122/64 ($\pm 19/12$), and 129/75 ($\pm 14/9$) mmHg and the baseline HR was 82 (± 9), 64 (± 11), and 71 (± 16) bpm, respectively. Plots of MPRi normalized to the rate-pressure-product for the three groups are shown in Fig. 3. Significant differences were noted between OHT and normal controls and between OHT and MI controls, while the difference between normal and MI controls was not significant.

Late gadolinium enhancement

Five post-OHT patients had qualitative evidence of LGE. In none of them was the pattern of LGE consistent with prior myocardial infarction, i.e. subendocardial or transmural LGE in a coronary territory. The relationships between MPRi and GLS with quantitative burden of LGE were both weak (Fig. 4), without reaching statistical significance, but demonstrated opposite trends: a positive trend with MPRi and a negative trend with GLS.

Endomyocardial biopsy

19 of 20 post-OHT patients experienced at least one episode of cellular rejection and two patients experienced humoral rejection. There were no clear relationships between MPRi or GLS with rejection parameters. Specifically, only weak correlations without statistical significance were noted between MPRi or GLS and the total number of cellular rejection episodes ($R = 0.16$, $P = 0.50$; $R = 0.32$, $P = 0.41$) as well as between MPRi or GLS and the total combined number of cellular and humoral rejection episodes ($R = 0.14$, $P = 0.55$; $R = 0.25$, $P = 0.45$). There was no significant difference between the MPRi or GLS in patients with no or any history of mild rejection (Grade 0, 1A, 1B) versus patients with moderate or severe rejection (Grade 2, 3A, 3B, 4) ($P = 0.65$; $P = 0.37$). Additionally, there was no difference in the mean MPRi or GLS of patients with any history of Grade 0 or 1A rejection and patients with Grade 1B rejection or higher ($P = 0.80$; $P = 0.78$).

Coronary allograft vasculopathy

The mean TIMI frame count for the post-OHT sample was 43 ± 16 frames. There was a moderate correlation between MPRi and TIMI frame count of the LAD ($R = -0.68$, $P = 0.0009$) (Fig. 5, top) and between MPRi and time from OHT to vCMR ($R = 0.50$, $P = 0.03$). In multivariate analysis controlling for the time from OHT to vCMR, the correlation between MPRi and TIMI frame count persisted ($R = 0.70$, $P = 0.003$). MPRi was higher in patients with TIMI frame count of 0–30 and also 31–45, compared to those with 46 frames (Fig. 5, middle). Additionally, MPRi in patients with CAV 0 or 1 (not significant or mild, $N = 17$) was higher than in patients with CAV 2 or 3 (moderate or severe, $N = 3$) (Fig. 5, bottom). There was a good correlation between GLS and TIMI frame count of the LAD (Fig. 6, top) and a significant difference was noted in GLS between CAV grades (Fig. 6, bottom).

Echocardiography

In the OHT group, mean LVEF measured by TTE and vCMR was $63 \pm 6\%$ and $60 \pm 6\%$, and there were no regional LV wall motion abnormalities detected on either imaging modality. Mean GLS was $-16.3 \pm 2.9\%$, which is outside the expected normal range [26]. Of note, a good correlation was observed between MPRi and GLS (Fig. 7).

Discussion

While vCMR has been shown to accurately diagnose patients with coronary artery disease of the native heart [30–33], less is known about the transplanted heart. Previous small vCMR studies have shown that abnormal MPRi or other vCMR parameters are associated with CAV diagnosed by invasive coronary angiography and/or endomyocardial biopsy [13, 34–38]. However, potential confounding factors have not been systematically investigated. Moreover, GLS is a well-documented and sensitive marker of myocardial deformation [39]. In post-OHT patients, GLS has been previously noted to be a prognostic marker of adverse outcomes and recently has been shown to play a role in patients with CAV compared to other echocardiographic parameters such as LVEF or tissue Doppler parameters of LV function [40, 41]. Similar to vCMR-derived MPRi, little is known about the potential confounders of abnormal GLS in this patient population. There are several potential

explanations for the reduced MPRi and GLS magnitude noted in the post-OHT population, including CAV, rejection, myocardial scar/fibrosis, and allograft dysfunction. To our knowledge, this is the first study that comprehensively evaluated these factors that could potentially reduce MPRi or GLS magnitude and thus confound the association between these parameters and CAV. We found that CAV is the likely explanation for reduced MPRi and GLS magnitude, rather than the other aforementioned factors.

While previous studies have examined myocardial perfusion reserve with other non-invasive techniques such as PET, few studies have used vCMR in post-OHT patients. In a PET investigation of post-OHT patients free of epicardial CAD, MPR was impaired early after OHT (< 3 months), but ultimately recovered > 9 months post-transplantation [5]. In another PET study of post-OHT patients without epicardial CAD, resting myocardial perfusion was highest 1 year after transplantation before subsequently declining [6]. Our study shows that MPR is abnormally reduced in the late post-transplant period, compared to normal and post-MI controls.

It is known that nearly 50% of patients 10 years post-OHT have evidence of CAV [42]. CAV is postulated to impact the coronary microcirculation potentially before the development of epicardial disease. In this study, a correlation between surrogate markers of CAV and MPRi and GLS was noted. Using the ISHLT grading criteria, patients with no or mild CAV had a higher MPRi compared to those with more significant CAV. Additionally, we confirmed the results of other smaller studies that showed that elevated TIMI frame counts correlated with microvascular disease in both native and transplanted hearts [3, 43–45]. We also found that worsening in MPRi and GLS was associated with worsening in TIMI frame counts. However, unlike our study, none of the previous studies robustly excluded other potential explanations for abnormal MPRi.

Specifically, in our study, quantitative LGE did not correlate with either MPRi or GLS. Previous studies have yielded mixed results when assessing the correlation between LGE and CAV, with some suggesting no relationship [13, 34], while others describing a potential association [46]. In contrast, unique to our study is the fact that we also explored the relationship between rejection data and MPRi and GLS. While several previous studies have suggested a relationship between CAV and historical rejection episodes, these studies have not measured MPRi, and conflicting data exist regarding this relationship [35, 47–49]. With respect to GLS, several previous studies have noted an association between GLS and rejection [15, 18, 50, 51]. These studies, however, did not systematically examine CAV as a potential explanation for reduced GLS. Since CAV is likely due to a combination of immunological and non-immunological mediated factors, there is likely some downstream effect with multiple episodes of rejection and the development of CAV. Nevertheless, we did not observe any relationship between the total number or severity of rejection episodes and MPRi or GLS.

While abnormal LVEF has prognostic value in post-OHT patients, those with normal LVEF are more difficult to risk stratify. In our patients without clinically evident allograft dysfunction, GLS and MPRi were found to be better correlated with surrogate markers of CAV, and not other potential confounders. Interestingly, we also observed a correlation

between GLS and MPRi. This relationship may be explained by the fact that perfusion abnormalities of the subendocardium are more likely to be detected with GLS, which is highly dependent on the longitudinal fibers in the subendocardial layer of the heart. Further studies specifically examining subendocardial MPRi and GLS may show a stronger correlation. Also, additional studies evaluating the role of CMR derived strain either using strain-encoded MRI or feature tracking may add incremental value to myocardial perfusion analysis.

The use of non-invasive imaging has been advocated for the detection of CAV. The diagnosis of CAV can allow for treatment with more aggressive immunosuppression or novel medical therapies to halt, or at least slow down, its progression [52]. Our findings suggest that both vCMR and TTE may be potentially useful as non-invasive tools for the diagnosis of late CAV. Further work to examine patients in the early post-OHT period are needed.

Limitations

There are several limitations to the study. The study is retrospective with a relatively small sample size. Additionally, our sample population is relatively heterogeneous in terms of their time course post-transplant. While we sought to examine patients' late post-OHT, there was nonetheless a wide range of time. Ideally all imaging modalities would have been performed within a short time window, but due to the retrospective analysis in our study, this was not the case. Also, at the time of the study, T1 mapping was not routinely performed, which has been shown to be useful to detect scar/fibrosis. Furthermore, The LGE contrast agents, while not approved by the Food and Drug Administration for CMR, were widely used in the United States and Europe at the time of this study. Also, while invasive coronary angiography with IVUS is the "gold standard" to diagnose CAV, our lab was not routinely performing IVUS at the time of the study. Therefore, we utilized another marker of microcirculatory dysfunction, namely TIMI frame count, as a surrogate for CAV [3]. Lastly, in our vCMR protocol, imaging was first performed under hyperemic conditions, while resting perfusion evaluation was performed after the reversal of hyperemia with aminophylline. Although this sequence has been shown to underestimate MPR [53], this is unlikely to have impact on our results since this protocol was used in all patients and controls. In our MPR calculations, we used the upslope technique rather than a fully quantitative technique involving deconvolution, which could have been more accurate. However, the fact that we were able to find a relationship despite using the upslope technique only supports the notion that the relationship between MPR and CAV is real and possibly underestimated in our study.

Conclusion

To the best of our knowledge, this is the first multimodality imaging study examining a variety of hypotheses governing reduced MPRi and GLS in a population of patients late after transplantation. We found that MPRi and GLS are both abnormal in > 1-year post-OHT patients, which is likely due to underlying CAV, but is unrelated to rejection episodes, presence of LGE, or reduced LVEF. Assessment of MPRi or GLS may be a useful strategy to detect CAV.

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Abbreviations

vCMR	Vasodilator cardiac magnetic resonance
MPRI	Myocardial perfusion reserve index
OHT	Orthotopic heart transplant
CAV	Coronary allograft vasculopathy
LGE	Late gadolinium enhancement
GLS	Global longitudinal strain

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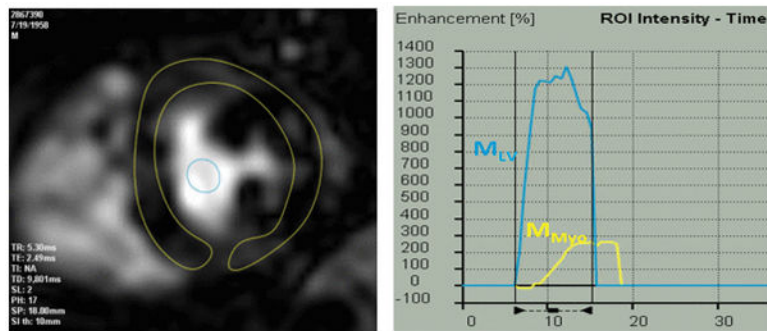


Fig. 1. Vasodilator stress CMR image obtained in a post-OHT patient with regions of interest drawn in the myocardium and the left ventricular cavity (left) used to generate regional time-intensity curves (right), from which upslopes were derived for MPR calculation (see text for details)

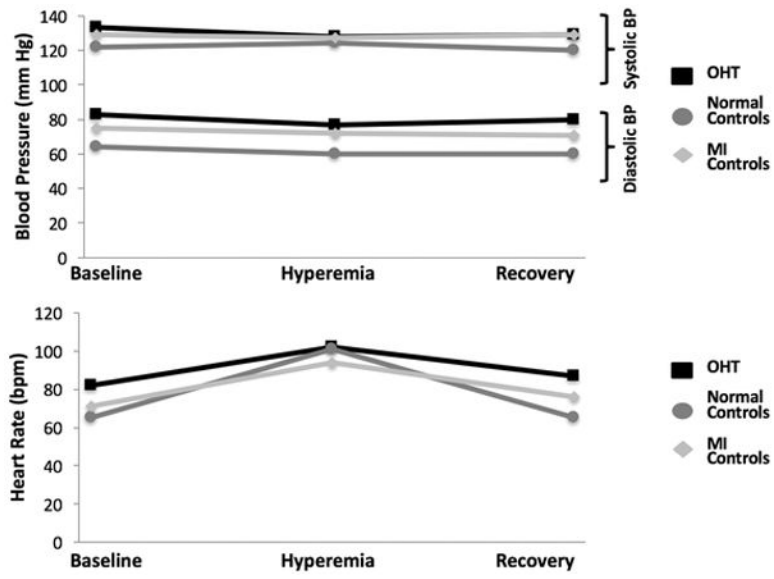


Fig. 2. Hemodynamic parameters (blood pressure and heart rate) in response to regadenoson during vCMR at baseline, hyperemia, and recovery

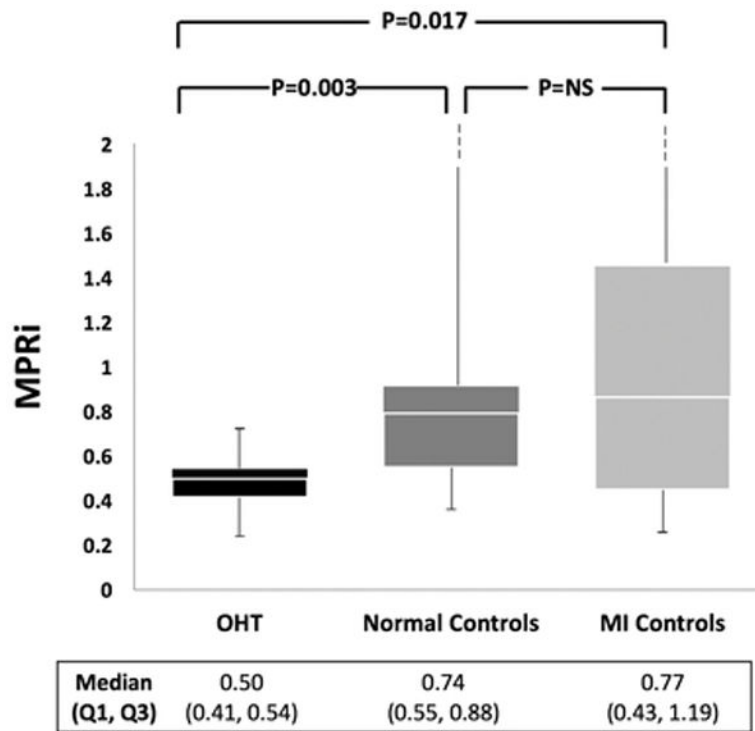


Fig. 3. Myocardial perfusion reserve index (MPRI) derived from vCMR of study population and control groups

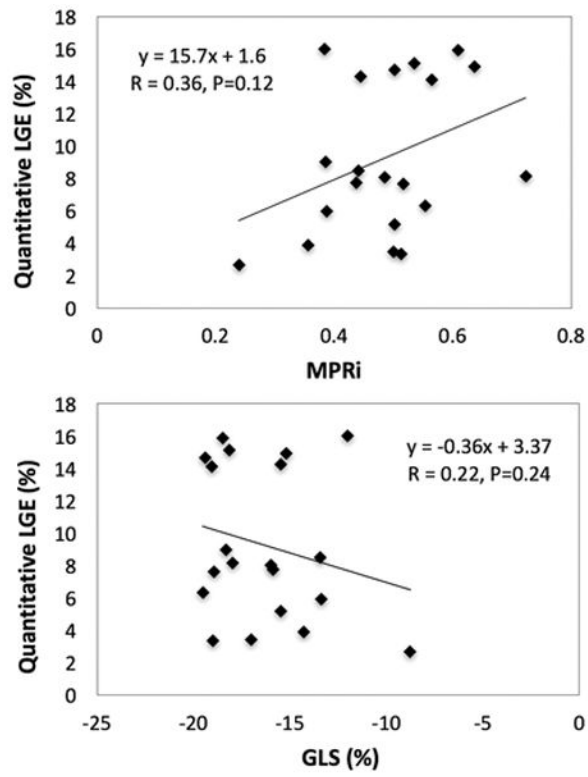


Fig. 4. Relationship between quantitative late gadolinium enhancement (LGE) and MPRi or GLS

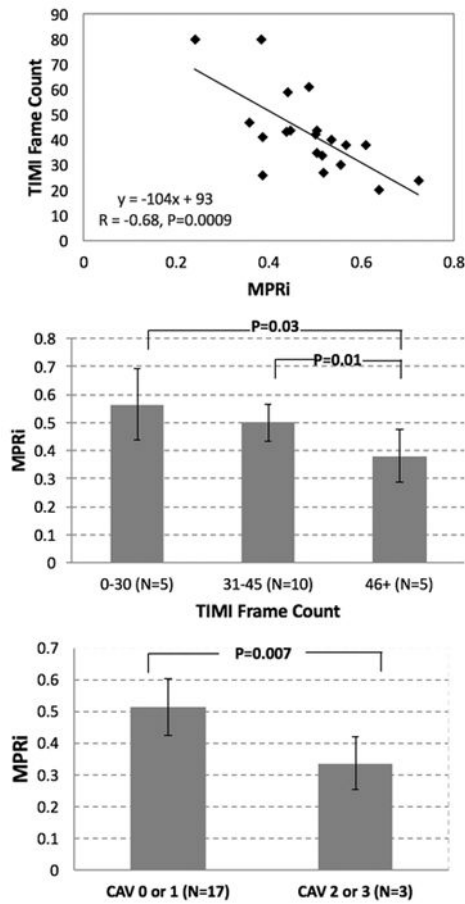


Fig. 5. Relationship between MPRI and thrombolysis in myocardial infarction (TIMI) frame count represented continuously (top) and grouped according to TIMI frame count 0–30, 31–45, and 46+ frames (middle). Relationship between MPRI and International Society for Heart & Lung Transplantation (ISHLT) grading of coronary allograft vasculopathy (CAV) (bottom)

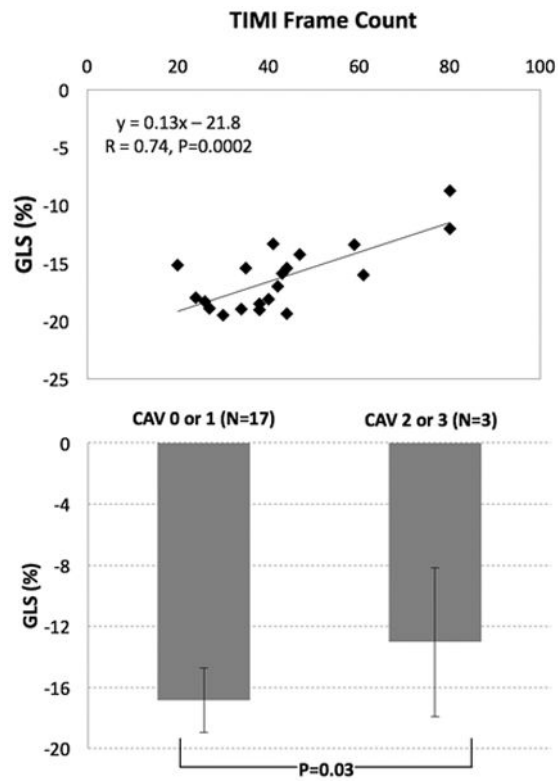


Fig. 6. Relationship between global longitudinal strain (GLS) and TIMI frame counts (top) and CAV grades (bottom)

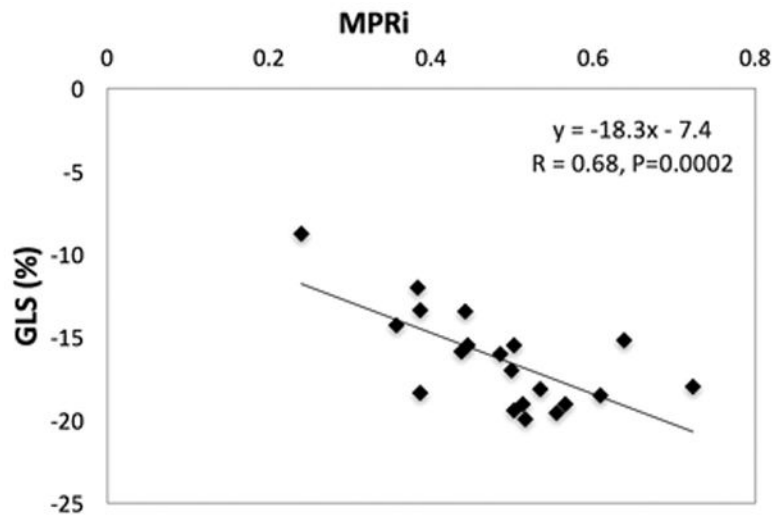


Fig. 7.
Relationship between MPRi and GLS

Table 1

Patient demographics of study population and control groups

Patient characteristics	OHT	Normal controls	MI controls
Total patients	20	10	20
Male	14 (70%)	6 (60%)	9 (45%)
Mean age \pm SD (years)	57 \pm 12	42 \pm 13	65 \pm 11
Race			
Caucasian	11 (55%)	10 (100%)	10 (50%)
African American	9 (45%)	0 (0%)	10 (50%)
LV systolic dysfunction	0 (0%)	0 (0%)	10 (50%)
Hypertension	18 (90%)	0 (0%)	17 (85%)
LDL (mg/dl)	90 \pm 36	68 \pm 10	80 \pm 38
Diabetes	10 (50%)	0 (0%)	6 (30%)
Chronic kidney disease (GFR < 60 ml/min/1.73 m ²)	8 (40%)	0 (0%)	7 (35%)
Mean GFR	66 \pm 22	101 \pm 17	94 \pm 75
Overweight (BMI > 25)	17 (85%)	1 (10%)	14 (70%)
Current/former smoker	9 (45%)	1 (10%)	10 (50%)

OHT orthotopic heart transplant, *MI* myocardial infarction

Table 2

Vasodilator cardiovascular magnetic resonance imaging (vCMR) characteristics of study population and control groups

vCMR characteristics	OHT	Normal controls	MI controls	P-value (3-way comparison)
LV ejection fraction (%)	59.9 ± 6.5 [#]	63.0 ± 5.3 [^]	50.8 ± 15.0 ^{#,^}	< 0.01
LV end systolic index (ml/m ²)	26.5 ± 10.4	33.4 ± 11.1	48.5 ± 34.5	0.02
LV end diastolic index (ml/m ²)	62.5 ± 15.8 ^{*,#}	90.0 ± 30.0 [*]	90.6 ± 34.9 [#]	< 0.01
LV mass index (mg/m ²)	58.4 ± 13.3 [*]	35.4 ± 18.4 ^{*,^}	64.6 ± 21.8 [^]	< 0.01

OHT orthotopic heart transplant, MI myocardial infarction

* P < 0.05 for OHT versus normal controls,

[#] P < 0.05 for OHT versus MI controls,

[^] P < 0.05 for normal controls versus MI controls