We sought to determine the ability of quantitative myocardial perfusion reserve index (MPRI) by cardiac magnetic resonance (CMR) and high-sensitive troponin T (hsTnT) for the prediction of cardiac allograft vasculopathy (CAV) and cardiac outcomes in heart transplant (HT) recipients. In 108 consecutive HT recipients (organ age 4.1 ± 4.7 years, 25 [23%] with diabetes mellitus) who underwent cardiac catheterization, CAV grade by International Society for Heart & Lung Transplantation (ISHLT) criteria, MPRI, late gadolinium enhancement (LGE) and hsTnT values were obtained. Outcome data including cardiac death and urgent revascularization ("hard cardiac events") and revascularization procedures were prospectively collected. During a follow-up duration of 4.2 ± 1.4 years, seven patients experienced hard cardiac events and 11 patients underwent elective revascularization procedures. By multivariable analysis, hsTnT and MPRI both independently predicted cardiac events, surpassing the value of LGE and CAV by ISHLT criteria. Furthermore, hsTnT and MPRI provided complementary value. Thus, patients with high hsTnT and low MPRI showed the highest rates of cardiac events (annual event rate = 14.5%), while those with low hsTnT and high MPRI exhibited excellent outcomes (annual event rate = 0%). In conclusion, comprehensive "bio-imaging" using hsTnT, as a marker of myocardial microinjury, and CMR, as a marker of microvascular integrity and myocardial damage by LGE, may aid personalized risk-stratification in HT recipients.

Abbreviations: CAD, coronary artery disease; CAV, cardiac allograft vasculopathy; CCT, cardiac computed tomography; CMR, cardiac magnetic resonance; hsTnT, high-sensitive troponin T; HT, heart transplant; IDI, discrimination improvement; ISHLT, International Society for Heart & Lung Transplantation; IVUS, intravascular ultrasound; LGE, late gadolinium enhancement; MPRI, myocardial perfusion reserve index; NTproBNP, N-terminal pro-brain natriuretic peptide; PCI, percutaneous coronary intervention; ROC, receiver operating characteristics.
Lung Transplantation (ISHLT) class > Ia was excluded by histological analysis (6). HT recipients, who had contraindications to gadolinium, adenosine or CMR, such as metal implants, or MDRD < 30 mL/min/1.73 m² were not enrolled. All procedures complied with the Declaration of Helsinki, were approved by our local ethic committee and all patients gave written informed consent. Part of our patients (n = 63 of 108, 58% of the present cohort) were included in previous reports, where the ability of angiographic myocardial blush grade was investigated to predict cardiac outcomes in transplant recipients (7).

CMR examination

HT recipients were examined in a clinical 1.5-T whole-body CMR scanner Achieva system (Philips Medical Systems, Best, the Netherlands). This is part of our institutional protocol, performed in HT recipients, as described previously (7–9). Briefly, a standardized imaging protocol was used, aiming at the assessment of baseline parameters of the left ventricle such as left ventricular (LV) diameters, septal and lateral wall thickness and, ejection fraction using cine imaging. Myocardial perfusion reserve was assessed during pharmacologic hyperemia with adenosine in all patients. By this approach, a mean myocardial perfusion reserve index (MPRI) was calculated by dividing the blood pool corrected upslope at pharmacologic hyperemia through the blood pool corrected upslope at rest in 16 myocardial segments, which served as a semi-quantitative estimate of the global perfusion reserve in each patient (8,10). Late gadolinium enhancement (LGE) images were scored visually using a 17-segment model. Hereby, both ischemic (infarct-related) and atypical noninfarct-related patterns of LGE were analyzed (11).

Cardiac catheterization and assessment of CAV

Coronary angiograms were performed in a standardized fashion, as described previously (7). Coronary vessels were classified by coronary angiography, based on the ISHLT nomenclature for CAV (12).

Biomarkers

Blood samples were drawn from a peripheral vein before the CMR examination and samples were stored immediately at −80°C. HsTnT was measured using the new hsTnT quantitative electrochemiluminescence immunoassay (Cobas 411; Roche Diagnostics, Mannheim, Germany) as described previously (13). A concentration of 14 ng/L has been identified as the 99th percentile of a healthy reference population with a coefficient of variation of <10%.

Definition of study end points

Study nurses unaware of the CMR imaging and coronary angiography results contacted each subject and the date of this contact was used for the calculation of the follow-up time duration. Cardiac death (death due to intractable heart failure or myocardial infarction or sudden death due to infarction or severe arrhythmia and all-cause mortality were recorded. Other cardiac events included nonfatal myocardial infarction and percutaneous coronary intervention (PCI). The reasons for PCI (myocardial infarction, unstable angina or heart failure symptoms including progressive dyspnea as an equivalent of angina in HT recipients and elective PCI during surveillance heart catheterization due to angiographically significant coronary artery stenosis (≥70%) in combination with the presence of inducible ischemia by stress echocardiography, CMR or fractional flow reserve) were also reported in this context. Our primary analysis included the combined end point of cardiac death, nonfatal myocardial infarction and clinically indicated PCI. A secondary analysis was conducted for hard cardiac events, including cardiac death, myocardial infarction and urgent PCI.

Statistical analysis

Analysis was performed using commercially available software MedCalc9.3 (MedCalc software, Mariakerke, Belgium). Continuous variables were expressed as mean ± standard deviation and categorical variables as proportions. Unpaired Student t-tests were used to compare continuous variables. Group differences between continuous variables were tested using analysis of variance with Bonferroni adjustment for multiple comparisons. Differences between ordinal variables were tested using the exact Mann–Whitney test, and differences between nominal variables were assessed using the Fisher exact test. All tests were two-tailed. Receiver operating characteristics (ROC) were used to determine the prognostic value of hsTnT and MPRI for the prediction of outcomes. Subsequently, patients were separated in two groups according to ROC optimized threshold values, and corresponding Kaplan–Meier curves were generated for the estimation of the primary and secondary end point. Furthermore, the association between clinical parameters with CMR and angiography was investigated using Cox proportional-hazards models and multivariable procedures. Discrimination improvement (IDI) values were calculated using the “survIDINRI” software package. Intra- and inter-observer variability for quantification analysis of MPRI were calculated by repeated analysis of 30 randomly selected patients by two observers with more than 5 years experience in cardiovascular imaging who were blinded to clinical and CMR data (INPH, GK). Differences were considered statistically significant at p < 0.05.

Results

Clinical outcomes

During a median follow-up duration of 4.2 ± 1.4 years, 18 patients experienced cardiac events. Seven patients had hard cardiac events including four with cardiac death and three who underwent urgent PCI due to myocardial infarction (n = 2) or unstable angina pectoris (n = 1). Eleven patients underwent revascularization procedures during surveillance heart catheterization. Five patients died of noncardiac reasons (three due to sepsis, two due to cerebral-vascular complications).

Patient characteristics are illustrated in Table 1. 106 of 108 (98%) patients exhibited preserved LV function (ejection fraction >50%). Similar baseline characteristics were present in patients with versus those without cardiac events. Patients with hard cardiac events exhibited higher values of hsTnT and septal wall thickness compared to those without cardiac events. In addition, patients with revascularization procedures exhibited higher CAV grades compared both to those with hard and without cardiac events.

Relation of MPRI to CAV and cardiac outcomes

Patients with hard cardiac events and revascularization procedures exhibited markedly lower MPRI compared to those without cardiac events (Figure 1A). Increasing MPRI values on the other hand, were observed with decreasing CAV by ISHLT criteria (Figure 1B). Furthermore, a weak inverse correlation was observed between MPRI and hsTnT (r = −0.21, p = 0.03).

Survival analysis

ROC optimized cutoff values for hsTnT and MPRI (Figure S1) were selected for survival analysis, which can be appreciated in Figure 2. Corresponding cumulative event rates are also provided. Hereby, hsTnT and MPRI sharply
discriminated between patients with and without cardiac events (Figure 2A and 2B). In addition the two markers exhibited complementary value for the assessment of hard and all cardiac events (Figure 2C and 2D). Thus, patients with both high hsTnT and low MPRI showed the highest rates of hard and all cardiac events (annual event rates = 7.7% and 14.5%, respectively), followed by those with either high hsTnT or low MPRI (annual event rates = 1.2% and 2.2%, respectively), while those with both low hsTnT and high MPRI exhibited excellent outcomes without
occurrence of any single cardiac event (annual event rates of 0% for both).

Univariate, multivariable and IDI analysis
By univariate analysis CAV by ISHLT criteria, N-terminal pro-brain natriuretic peptide (NTproBNP), hsTnT and LGE and myocardial perfusion reserve by CMR were significantly associated with outcomes (Table 2). By multivariable analysis, hsTnT and MPRI provided the most robust prediction of both hard and all cardiac events, surpassing the value of organ age, LV hypertrophy, LGE and CAV by ISHLT criteria (Table 3).

Using a series of Cox models hsTnT and MPRI offered incremental information for the assessment of the primary and secondary end point by chi-square and IDI analysis (Figure 3A and 3B).

Representative CMR perfusion images (Figure 4A and 4B) in a patient with markedly reduced MPRI of 1.1 (Figure 4C and 4D). This patient also exhibited infarct-typical LGE and increased hsTnT of 40 pg/mL, albeit only mild CAV (<50% stenosis) by angiography (Figure 4E and 4F). During 1.3 years of follow-up, he underwent urgent PCI.

Prediction of CAV progression
 Ninety-one of 108 patients underwent more than one surveillance coronary angiographic study after the index CMR scan (mean time duration of 2.1 ± 1.6 years). MPRI was significantly higher in patients with stable CAV between the two invasive procedures (n = 82), compared with those who showed significant CAV progression, converting from absent/mild to moderate/severe CAV (n = 9). A nonsignificant trend was observed in the same context for hsTnT (Figure S2).

Observer agreement and time spent
Quantification of MPRI yielded intra- and inter-observer variability of 9% and 12%, respectively. Time spent for MPRI quantification was 17.8 ± 3.1 min per patient.

Discussion
To the best of our knowledge our study is the first to simultaneously investigate the value of cardiac troponins and myocardial perfusion by CMR for the prediction of cardiac outcomes in HT recipients. Cardiac troponins were assessed using the high sensitivity assay, which was also recently used in the PEACE study (Prevention of Events With Angiotensin-Converting Enzyme Inhibitor Therapy) (4), whereas a standardized semi-quantitative approach was applied for the assessment of MPRI. Hereby, we demonstrated that

(i) Noninvasive MPRI by CMR is associated both with CAV by ISHLT criteria and with cardiac outcomes,
(ii) HsTnT and MPRI independently predict cardiac outcomes but also demonstrate complementary value to each other. Thus, patients with low hsTnT and high MPRI exhibit excellent outcomes, whereas patients with high hsTnT and low MPRI show extremely poor outcome (mean annual event rate of 14.5%).
(iii) MPRI is also predictive for CAV progression.

Such a comprehensive bio-imaging approach presented herein may provide personalized risk assessment and aid tailoring diagnostic procedures (reduce the necessity for frequent invasive procedures) or specific immunosuppressive pharmacologic treatments according to the individual risk for future cardiac events in HT recipients.

Previous studies for detection of CAV using CMR
Myocardial perfusion imaging by CMR has been validated as a versatile noninvasive clinical tool for the diagnostic
classification and risk-stratification of patients with CAD (reviewed in [14]). Fewer studies however, investigated the role of stress perfusion CMR for the detection of CAV. In this regard, we and others previously reported that the myocardial perfusion reserve during vasodilator stress CMR is associated with CAV in HT recipients (8,15). In addition, Miller et al (16) recently demonstrated, using CMR, intravascular ultrasound (IVUS) and fractional flow reserve measures in HT recipients, that MPRI is independently associated with both epicardial and microvascular components of CAV, surpassing the value of surveillance coronary angiography for early CAV detection.

In the present study the relation between CAV and MPRI was confirmed and association between MPRI and cardiac outcomes could be established. Interestingly, the cutoff value of <1.3 used for the detection of patients with poor outcomes is close to 1.4, which was selected as cutoff value for CAV detection (8). Different patterns of both infarct-related and infarct-atypical LGE on the other hand, were previously demonstrated in HT recipients and were shown to be associated with the degree of CAV (11). In our study, LGE was observed in 33 (31%) patients and a trend was noted for cardiac events in the presence of either typical or atypical LGE patterns. However, using multivariable analysis LGE did not prove to be an independent predictor of cardiac events. Septal hypertrophy on the other hand was significantly associated with cardiac events, while a nonsignificant trend was observed for LV mass. This is in line with previous observation, where LV hypertrophy was identified as an independent risk for cardiovascular outcomes after HT (17).

We and others previously proposed other invasive and noninvasive imaging modalities including echocardiography, cardiac computed tomography (CCT) and IVUS for monitoring CAV in HT recipients (18), reviewed in [19]). However, CMR is better suited for the serial evaluation of such patients due to (i) its tomographic nature, ensuring reproducibility of serial measurements, (ii) its noninvasive nature and (iii) the absence of radiation exposure for the patients.

Figure 2: Kaplan–Meier analysis. Both myocardial perfusion reserve index (MPRI) (A) and high-sensitive troponin T (hsTnT) (B) were predictive for cardiac events separately. Patients with low hsTnT and high MPRI exhibited excellent outcome with no single cardiac event during the follow-up duration. Patients with high hsTnT and low MPRI on the other hand, demonstrated extremely poor outcome (mean annual event rates of 7.7% for hard cardiac and of 14.5% for all cardiac events) (C–D).
Biomarkers for the detection of CAV
Cardiac troponins, which are highly sensitive and specific markers of myocardial injury and established markers of cardiovascular risk, were previously shown to predict development of CAV, graft failure and cardiac mortality in HT recipients (20). In the same line, and using a highly sensitive assay, we recently demonstrated that measurements of hsTnT predict both short- and long-term survival after HT (5). Thus, patients with a cutoff value of hsTnT ≥ 33 pg/mL measured within the first 6 weeks after HT exhibited a more than sixfold risk for cardiac mortality during the following 5 years compared to patients with hsTnT < 33 pg/mL. Of course elevated hsTnT values may be attributed to several other causes apart from CAV, such as increased myocardial strain due to volume or pressure overload and myocardial hypertrophy. This is also indicated by the weak association between hsTnT and impaired myocardial perfusion reserve, as noted in our study. In addition, other conditions, such as acute allograft rejection, impaired cell membrane integrity due to systemic inflammatory response or apoptosis and extracardiac disease such as end-stage renal failure may result to hsTnT elevation in the absence of significant CAV (21).

Combination of biochemical markers with imaging
Fewer studies have combined biomarkers with imaging modalities aiming at a more comprehensive assessment of CAV in HT recipients so far. In this regard, an association between hsTnT and coronary intimal thickness was demonstrated using optical coherence tomography, which exhibited better observer variability than IVUS for the determination of intimal thickness (22). However, both

Table 2: Univariate value of demographic, clinical, hsTnT, NTproBNP and CMR data for the prediction of hard cardiac events and revascularization procedures

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Prediction of hard cardiac events</th>
<th></th>
<th>Prediction of all cardiac events</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p-Value</td>
<td>Hazard ratios</td>
<td>Confidence interval</td>
<td>p-Value</td>
</tr>
<tr>
<td>Age (years)</td>
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<td>0.99</td>
<td>0.94–1.05</td>
<td>NS</td>
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<td>Organ age (years)</td>
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<td>NS</td>
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<td>0.17–4.51</td>
<td>NS</td>
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<td>Arterial hypertension, n (%)</td>
<td>NS</td>
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<td>0.08–1.61</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperlipidemia or statin therapy, n (%)</td>
<td>0.003</td>
<td>0.08</td>
<td>0.02–0.41</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
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<td>0.09–6.16</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
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<td>0.24–6.30</td>
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</tr>
<tr>
<td>BMI (kg/m²)</td>
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<td>0.77–1.12</td>
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<tr>
<td>Ejection fraction (%)</td>
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<td>0.91–1.15</td>
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<td>Septal wall thickness (mm)</td>
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<td>0.69</td>
<td>0.46–1.05</td>
<td>NS</td>
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<td>LV mass (g)</td>
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<td>0.98</td>
<td>0.94–1.02</td>
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<td>Infarct-typical LGE</td>
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<td>1.89</td>
<td>0.23–15.6</td>
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<td>Infarct-atypical LGE</td>
<td>0.03</td>
<td>5.19</td>
<td>1.16–23.0</td>
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</tr>
<tr>
<td>LGE (typical and atypical patterns)</td>
<td>0.03</td>
<td>6.28</td>
<td>1.22–32.2</td>
<td>0.06</td>
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<tr>
<td>CAV by ISHLT criteria (0–3)</td>
<td>NS</td>
<td>0.86</td>
<td>0.22–3.42</td>
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</tr>
<tr>
<td>NTproBNP (pg/mL)</td>
<td>0.04</td>
<td>1.0</td>
<td>1.00–1.001</td>
<td>NS</td>
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<tr>
<td>HsTnT (pg/mL)</td>
<td>0.005</td>
<td>1.04</td>
<td>1.01–1.08</td>
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<tr>
<td>MPRI</td>
<td>0.006</td>
<td>0.0007</td>
<td>0.00–0.012</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CAV, chronic allograft vasculopathy; CMR, cardiac magnetic resonance; HsTnT, high-sensitive troponin T; ISHLT, International Society for Heart & Lung Transplantation; LGE, late gadolinium enhancement; LV, left ventricular; MPRI, myocardial perfusion reserve index; NTproBNP, N-terminal pro-brain natriuretic peptide.

Table 3: Multivariable value of organ age, septal wall thickness, CAV, hsTnT and myocardial perfusion reserve index (MPRI) for the prediction of hard cardiac events and revascularization procedures

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Prediction of hard cardiac events</th>
<th></th>
<th>Prediction of all cardiac events</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>p-Value</td>
<td>Hazard ratios</td>
<td>Confidence interval</td>
<td>p-Value</td>
</tr>
<tr>
<td>Septal wall thickness (mm)</td>
<td>NS</td>
<td>0.64</td>
<td>0.36–1.12</td>
<td>NS</td>
</tr>
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<td>CAV by ISHLT criteria (0–3)</td>
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<td>0.19–7.19</td>
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<tr>
<td>LGE (typical and atypical patterns)</td>
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<td>0.41–23.2</td>
<td>NS</td>
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<td>NTproBNP (pg/mL)</td>
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<td>0.99–1.00</td>
<td>NS</td>
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<tr>
<td>HsTnT (pg/mL)</td>
<td>NS</td>
<td>1.01</td>
<td>0.97–1.05</td>
<td>0.01</td>
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<tr>
<td>MPRI</td>
<td>0.002</td>
<td>0.002</td>
<td>0.00–0.65</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CAV, chronic allograft vasculopathy; HsTnT, high-sensitive troponin T; ISHLT, International Society for Heart & Lung Transplantation; LGE, late gadolinium enhancement; NTproBNP, N-terminal pro-brain natriuretic peptide.
IVUS and optical coherence tomography are invasive techniques, which are therefore less appropriate for the serial evaluation of CAV compared to CMR.

To our knowledge we demonstrated for the first time that hsTnT and vasodilator stress CMR provide complementary value for the identification of patients at high risk for future cardiac events. Patients with both increased hsTnT and reduced myocardial perfusion reserve exhibited the highest rates of urgent PCI, cardiac death and coronary revascularization, whereas patients with low hsTnT and higher myocardial perfusion reserve exhibited excellent outcomes. Hereby, a cutoff value of 14 pg/mL was selected by ROC analysis, which is lower than that proposed in previous studies with HT patients, but identical to the upper reference limit of 14 pg/mL (99th percentile for hsTnT). This difference to previous HT studies may be attributed to the time point of hsTnT assessment, which was previously set within the first 6 weeks after HT, where inflammatory and immunologic processes may trigger hsTnT leakage from the transplanted heart, in contrast to the present study where hsTnT measures were assessed at a mean time of 4.1 years after HT.

**Potential pathophysiologic mechanisms**

Both in HT recipients and in patients with stable CAD increased hsTnT levels indicate severe myocardial injury or irreversible myocyte death, possibly caused by silent plaque rupture, microembolization and microvascular obstruction, which may precede the clinical manifestation of myocardial infarction (23). Interestingly, a recent optical coherence tomography study demonstrated the presence of complicated coronary lesions with intimal laceration, intraluminal thrombus and plaque ruptures in a significant proportion of asymptomatic HT recipients (24). This underlines our hypothesis, that repetitive plaque ruptures in HT recipients may cause chronic myocardial microinjury, reflected both by increased hsTnT blood levels and by the presence of LGE in such patients. The presence of both infarct-typical and atypical LGE patterns in patients with increased hsTnT levels and future cardiac events, however, indicate that further mechanisms apart from plaque rupture and microembolization may be involved in hsTnT leakage, including myocardial hypertrophy due to pressure overload and fibrosis due to hypertrophy and systemic inflammatory response. An overview of potential mechanisms of myocardial injury in HT recipients with CAV is given in Figure S3.

Our study has some limitations. First of all, the number of patients included in our study (n = 108), and the number of cardiac events (n = 7) and revascularization procedures (n = 11) was small. Furthermore, serial measures of MPRI and hsTnT were not available. IVUS and optical coherence tomography on the other hand were not used to evaluate the wall of coronary vessels, which may show increased intimal thickness despite normal appearance on coronary angiograms (25). Humoral rejection characterized by induced and complement-mediated activation of endothelial cells and macrophages, may also have a significant impact both on myocardial perfusion and on outcomes (26,27). In our study, however, the presence of antibody-mediated rejection was not systematically evaluated, which is a limitation, particularly in light of its potential impact on microvascular function (28).
Figure 4: Patient case. Representative cardiac magnetic resonance images (A–B) used for the assessment of myocardial perfusion in a heart transplant recipient with markedly reduced myocardial perfusion reserve index (≈1.1) (C–D). This patient exhibited infarct-typical late gadolinium enhancement and increased high-sensitive troponin T of 40 pg/mL, albeit only mild chronic allograft vasculopathy (<50% stenosis) by invasive angiography (E–F). At 1.3 years of follow-up, he underwent percutaneous coronary intervention due to unstable angina.
Conclusions

Our study demonstrates the complementary value of hsTnT and quantitative myocardial perfusion reserve during vasodilator CMR for the prediction of outcomes and of CAV progression in cardiac transplant recipients. Our findings implicate that apart from microembolization of atherosclerotic debris, other mechanisms like myocardial hypertrophy and inflammation may be involved in hsTnT elevation in such patients and underscore the potential value of such a comprehensive “bio-imaging” approach, aiding the personalized risk-stratification and prediction of future cardiac events.

Acknowledgments

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

References

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Figure S1: ROC analysis. Both hsTnT (A–B) and MPRI (C–D) were significantly associated with hard cardiac and with all cardiac events including revascularization procedures by ROC analysis. Cutoff values of hsTnT = 14 pg/mL and MPRI = 1.3 were selected for subsequent Kaplan–Meier analysis.

Figure S2: Association of MPRI and hsTnT with CAV progression. (A) MPRI was significantly higher in patients with stable CAV, compared with those who showed significant CAV progression, converting from absent/mild to moderate/severe CAV. (B) A similar albeit nonsignificant trend was observed for hsTnT.

Figure S3: Potential mechanisms of myocardial injury in HT recipients with CAV. Both in HT recipients increased hsTnT levels indicate myocardial injury, possibly caused by silent plaque rupture, microembolization and microvascular obstruction, which may precede the clinical manifestation of myocardial infarction and heart failure.