Cold ischaemic time and time after transplantation alter segmental myocardial velocities after heart transplantation†

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Abstract

OBJECTIVES: The aim of this study was to investigate changes in segmental, three-directional left ventricular (LV) velocities in patients after heart transplantation (Tx).

METHODS: Magnetic resonance tissue phase mapping was used to assess myocardial velocities in patients after Tx (n = 27) with normal LV ejection fraction (63 ± 5%) and those without signs of rejection. Regional wall motion and dysynchrony were analysed in relation to cold ischaemic time (150 ± 57 min, median = 154 min), age of the donor heart (35 ± 13 years, median = 29 years), time after transplantation (32 ± 26 months, median = 31 months) and global LV morphology and function.

RESULTS: Segmental myocardial velocities were significantly altered in patients with cold ischaemic times >155 min resulting in an increase in peak systolic radial velocities (2 of 16 segments, P = 0.03–0.04) and reduced segmental diastolic long-axis velocities (5 of 16 segments, P = 0.01–0.04). Time after transplantation (n = 8 patients <12 months after Tx vs n = 19 >12 months) had a significant influence on systolic radial velocities (increased in 2 of 16 segments, P = 0.01–0.04) and diastolic long-axis velocities (reduced in 5 of 16 segments, P = 0.02–0.04). Correlation analysis and multiple regression revealed significant relationships of cold ischaemic time (R = −0.384, P = 0.048), the donor heart’s age (β = 0.9, P = 0.01) and time from transplantation (β = −0.36, P = 0.03) with long-axis diastolic dyssynchrony.

CONCLUSIONS: Time after transplantation and cold ischaemic time strongly affect segmental systolic and diastolic motion in patients after Tx. The understanding of alterations in regional LV motion in the transplanted heart under stable conditions is essential in order to utilize this methodology in the future as a potentially non-invasive means of diagnosing transplant rejection.

Keywords: Magnetic resonance imaging · Heart transplantation · Myocardial velocities · Tissue phase mapping

INTRODUCTION

The analysis of regional myocardial function is of high interest in heart transplant recipients. Despite improvements in immunosuppressive therapy, transplant rejection and transplant vasculopathy still constitute major complications for patients after heart transplantation (Tx). However, the accurate diagnosis of acute transplant rejection and transplant vasculopathy is often difficult. Previous studies have shown that measures of global cardiac function such as left ventricular (LV) ejection fraction (LVEF) cannot be considered as sensitive markers. Myocardial biopsy which is still the gold standard for the diagnosis of rejection is limited by sample error, particularly during early rejection, as cellular infiltrates are known to be highly localized [1]. Moreover, coronary angiography has limited diagnostic value for transplant vasculopathy, and intravascular ultrasound is time-consuming and often not available for the screening for Tx vasculopathy. Despite their invasive nature, routine biopsies and coronary angiograms are still standard procedures in many centres due to the lack of reliable non-invasive diagnostic tools.

In this context, myocardial velocity analysis is promising. Previous studies provide evidence that depressed regional myocardial motion [1, 2], LV rotation [3] and diastolic function [2, 4] represent early indicators of transplant rejection, before global systolic function is reduced. In addition, reduced segmental systolic radial velocities have been associated with transplant vasculopathy [4]. There is growing evidence that even stable patients after Tx can demonstrate alterations in LV performance [5] due to remodelling within the transplanted heart [6].

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LV velocities and derived parameters based on tissue Doppler imaging were suggested as markers for LV contractility [7] and diastolic function [8]. However, tissue Doppler imaging is highly valuable in this context as it offers optimal temporal resolution, but it cannot assess all LV segments and, more importantly, does not permit the measurement of all myocardial velocity components, i.e. radial, long-axis and rotational motion. Speckle tracking echocardiography overcomes the limitations due to the dependency on the Doppler angle of tissue Doppler imaging and offers higher reproducibility. However, echocardiography is highly dependent on the experience of the examiner and the acoustic window of the patient, which may be limited after cardiac surgery. As an alternative, magnetic resonance imaging (MRI) applications have been developed to assess regional myocardial function. Previously applied techniques include tissue phase mapping (TPM), myocardial tagging or DENSE. TPM, which was used in this study, permits the direct quantification of LV dyssynchrony and segmental LV myocardial velocities along all three principle motion components with high resolution and full LV coverage [9, 10].

The aim of this study was to provide a comprehensive map of regional myocardial velocities in patients after Tx under stable conditions, and to evaluate the influence of multiple factors such as cold ischaemic time, age of the donor heart, time after transplantation, and global LV morphology and cardiac function.

METHODS

Study population

Patients’ characteristics are summarized in Table 1. Twenty-seven patients after Tx (50 ± 13 years, 6 females, LVEF 63 ± 5%, median = 63%) who were recruited consecutively in the out-patient clinics of the two study centres were included in the study. The inclusion criteria were as follows: written informed consent, >1 month after Tx, no history, prior episodes or signs of rejection, normal LVEF, invasive ruled out relevant coronary artery disease, no LV valvular Tx, no history, prior episodes or signs of rejection, normal LVEF, in

<table>
<thead>
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<th>Study cohort (N = 27)</th>
<th>Mean ± SD</th>
<th>Min</th>
<th>Max</th>
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<td>LVEF (%)</td>
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<td>LVSV (ml)</td>
<td>73 ± 21</td>
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Tx: transplantation; ischaemic time: cold ischaemic time; LV: left ventricle; EF: ejection fraction; EDV: end-diastolic volume; SV: stroke volume; SD: standard deviation; Min: minimum; Max: maximum.

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### Study population

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Written informed consent was obtained from all patients, and the study was approved by the local ethics boards of the recruiting centres (Feinberg School of Medicine, Northwestern University, Chicago, USA and University Heart Centre, Freiburg, Germany).

### Data acquisition

All measurements were performed using routine MR systems at both institutions (1.5 T Espree, Siemens, Germany at Northwestern University; 1.5 T Sonata and 3 T Trio, Siemens, Germany at Freiburg University). We acquired standard cine short-axis slices covering the complete LV without gap with a balanced Steady-state free precession (SSFP) (1.5 T) or FLASH sequence (3 T) in order to perform a standardized volumetric assessment of the LV. Data were acquired using a black blood k-space segmented gradient echo sequence with prospective ECG gating in basal, midventricular and apical short-axis planes (slice thickness, 8 mm). Velocity encoding was performed with velocity sensitivity of 15 cm/s in-plane (Freiburg University) respectively 25 cm/s in-plane (Northwestern University), e.g. for rotational and radial velocities and with 25 cm/s through-plane, e.g. long-axis velocities at both centres. In 8 patients, data were acquired during free-breathing using navigator respiration control (echo time (TE)/repetition time (TR) = 5.2/6.9 ms, spatial resolution 2.6 × 1.3 mm, slice thickness = 8 mm, temporal resolution 13.8 ms, flip angle = 15°) [9]. In 19 patients, data were acquired during breath hold using spatio-temporal imaging acceleration (k-t parallel imaging PEAK GRAPPA) with a net acceleration factor of Rnet = 3.6 (spatial resolution = 2.9 × 2.4 mm, slice thickness = 8 mm, flip angle = 15°, temporal resolution = 20–25 ms) [11].

### Data analysis

Data analysis was performed using a home-built tool programmed in Matlab (The Mathworks, Inc., Natick, MA, USA) and included manual segmentation of endo- and epicardial myocardial contours, followed by an automatic correction for bulk motion [12]. Furthermore, a correction for background phase offsets was performed. Three-directional myocardial velocities were measured in a Cartesian coordinate system orientated along the major axes of the imaging plane (x, y and z-directions). During post-processing, these three-directional phase contrast data were transformed into an internal cylindrical coordinate system, which was positioned at the centre of mass of the endocardial contour of the segmented left ventricle and which was calculated for each cardiac time frame and slice. As a result, the three principal LV motion components (radial, rotational and long-axis velocities) were derived from the measured three-directional myocardial velocities [12] (Fig. 1). Radial velocities were calculated as velocities towards the LV centre of mass, rotational velocities as velocities perpendicular to the endocardium and long-axis velocities as velocities orthogonal to the short-axis imaging planes. Peak systolic and diastolic long-axis and radial velocities as well as the times-to-peak velocities were extracted from velocity-time courses (Fig. 1) in 16 LV segments (American Heart Association [AHA] model, excluding the 17th apical segment, Fig. 2). Diastolic peak velocities refer to early
diastolic velocity peaks (Fig. 1). Results were mapped on the standardized AHA 16-segment bulls’ eye plots permitting a direct comparison between patients’ subgroups and LV segments (Fig. 2). In addition, peak systolic twist and peak diastolic untwist velocities (difference between apical and basal rotation) were calculated from the velocity-time courses for each subject.

Furthermore, in analogy to Yu et al. [13], we assessed four different parameters of dyssynchrony in each patient: systolic and diastolic long-axis dyssynchrony which were defined as the standard deviation (SD) of time-to-peak long-axis velocities over the 16 LV segments in the systole and the diastole of each individual and systolic and diastolic radial dyssynchrony being defined as the SD of time-to-peak radial velocities over all LV segments. Previous studies of TPM-derived myocardial velocities and time-to-peak velocities revealed a high reproducibility of the technique and low inter- and intraobserver variability [14].

Statistical analysis

All data are presented as mean ± SD unless stated otherwise. Comparisons between subgroups were performed by unpaired Student’s t-test for normally distributed values and Mann-Whitney U-test for values not normally distributed. The Kolmogorov-Smirnov test was used to test for normality. Peak twist, peak untwist and the dyssynchrony markers were correlated with the age of the patients and donor hearts, time after Tx, cold ischaemic time as well as parameters of LV morphology and function. Correlations were performed by a Pearson product-moment correlation for values normally distributed or a Spearman’s test for values not normally distributed. Further multiple linear regression analysis (as values were normally distributed) was performed using the Akaike Criterion (P ≤ 15.7%) to select variables. Statistical testing was performed using SigmaStat for Windows Version 3.10. Two-tailed tests with P < 0.05 were considered statistically significant.

To compare segmental velocities with respect to cold ischaemic times or time after Tx, the patient’s group was subdivided into two groups using the median values of cold ischaemic times and 12 months for time after Tx as a cut-off value for the separation of the two groups.

RESULTS

Study cohort

Clinical characteristics for all patients are summarized in Table 1. The age of the transplanted donor hearts (mean 36 ± 13 years, range: 14–60 years) was significantly lower compared with the patients’ age (mean 50 ± 12, range 21–66 years, P = 0.00008). The average time between Tx and MR imaging was 32 ± 26 (range 1–105) months. Mean cold ischaemic time was 150 ± 57 min ranging from 21 to 234 min. LVEFs, end-diastolic volumes and masses as derived from MRI cine images were within normal ranges. In 3 patients, complete volumetric MRI data could not be acquired due to patient compliance or technical reasons. As only three short-axis slices were acquired with TPM, we used echocardiography to calculate the LVEF of these patients. Echo-cardiography demonstrated an LVEF of 58 ± 2% in these patients. Twenty-three of the patients had received Basiliximab and 3 patients anti-thymocyte globulin as induction therapy. One patient had no induction therapy. 3% of the patients were on cyclosporine A, 26% on steroids, 74% on mycophenolate, 37% on tacrolimus and 30% on everolimus. 48% were treated with diltiazem, 7% with amlodipine, 70% with aspirin, 48% with ACE or AT1 receptor antagonists, 89% with statins and 48% with diuretics. 44% of the patients suffered from arterial hypertension, and 22% from diabetes.

Dyssynchrony and twisting motion

Peak systolic twist and diastolic untwist velocities as well as dyssynchrony parameters are summarized in Table 2. Patients’ age was
Segmental velocity analysis

Segmental radial and long-axis peak velocities in relation to cold ischaemic times are illustrated in Fig. 4. Systolic peak radial velocities in patients with cold ischaemic times longer than 155 min were generally higher and significantly increased in two segments (P < 0.05 for apico-septal and midventricular inferoseptal regions) compared with those with shorter cold ischaemic time. In diastole, patients with longer cold ischaemic times presented with substantially reduced segmental long-axis velocities (P < 0.01 for basal anterior and anterolateral, and P < 0.05 for midventricular anterior and anterolateral and for basal anteroseptal regions).

In Fig. 5, segmental radial and long-axis velocities are displayed for patients who were transplanted <12 months before the MRI examination compared with those with time after Tx >12 months. Patients in the first year after Tx showed increased systolic radial velocities (P < 0.05 for anteroseptal basal and P < 0.01 for inferoapical regions), whereas systolic long-axis velocities were reduced in lateral segments (P < 0.01 for anterolateral basal region). In diastole, long-axis velocities in patients were lower in the first year after Tx (P < 0.05 for basal septal and anterolateral and for midventricular lateral regions) compared with >12 months following Tx.

As myocardial velocity is influenced by age, it is important to note that neither the ages of the donors’ hearts nor the ages of the patients did differ significantly in the different patient groups. Donors’ and patients’ age was 33 ± 10 respectively 53 ± 10 years in patients <12 months after Tx and 33 ± 13 respectively 49 ± 13 years in patients >12 months after Tx. Donors’ age respectively patients’ age was 37 ± 13 and 50 ± 12 years with cold ischaemic times (CIT) ≤154 min vs 34 ± 12 and 51 ± 11 years with CIT >155 min.

Table 2: Peak twist/untwist velocities and dyssynchrony (N = 27)

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<th>Mean ± SD</th>
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<tr>
<td>Dyssyn_rad_sys (ms)</td>
<td>44.8 ± 14.9</td>
<td>12.0</td>
<td>73.1</td>
</tr>
<tr>
<td>Dyssyn_rad_dia (ms)</td>
<td>32.1 ± 13.9</td>
<td>14.7</td>
<td>63.7</td>
</tr>
<tr>
<td>Dyssyn_long_sys (ms)</td>
<td>36.0 ± 25.3</td>
<td>9.0</td>
<td>96.2</td>
</tr>
<tr>
<td>Dyssyn_long_dia (ms)</td>
<td>41.4 ± 24.4</td>
<td>10.1</td>
<td>97.7</td>
</tr>
<tr>
<td>V_twist (cm/s)</td>
<td>2.3 ± 0.8</td>
<td>0.9</td>
<td>4.8</td>
</tr>
<tr>
<td>V_untwist (cm/s)</td>
<td>−3.2 ± 1.1</td>
<td>−5.8</td>
<td>−0.7</td>
</tr>
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</table>

Peak twist and untwist velocities (V, Twist and V, Untwist) and radial (Dyssyn_rad) and long-axis dyssynchrony (Dyssyn_long). Twist and untwist were calculated as difference between apical and basal rotation. Dyssynchrony was defined as the SDs of time-to-peak radial and long-axis velocities over the 16 LV segments in systole and diastole. SD: standard deviations; Min: minimum; max: maximum.

DISCUSSION

Regional LV function analysis may be useful for an early diagnosis of acute transplant rejection or transplant vasculopathy in patients after Tx. The investigation of segmental LV function in transplant patients without complications and normal global cardiac function is an important prerequisite to improve the understanding of changes in global and regional LV performance and their association with factors such as cold ischaemic time or time after Tx in these patients. The results of our study showed that a reduction of segmental diastolic long-axis velocities was associated with increased cold ischaemic times in transplant recipients. Furthermore, in the first year after Tx, segmental systolic radial velocities were increased, whereas long-axis motion in systole and diastole was reduced compared with patients with time after Tx.
In addition, cold ischaemic time, time after Tx and the age of the donor heart affected long-axis diastolic dyssynchrony. These findings indicate that multiple factors associated with Tx itself alter LV function and need to be taken into account when investigating potential early markers of rejection or vasculopathy.

As we could demonstrate, it is feasible to detect regional differences of diastolic function and systolic long-axis myocardial motion using TPM. The possibility of a comprehensive evaluation of wall motion, including regional diastolic and long-axis motion, rotation and torsion with high reproducibility [14], might qualify this MRI method for follow-up studies aiming for intraindividual changes of myocardial function as possible early signs of transplant rejection. In these studies, the new imaging parameters should be correlated with the results of invasive procedures as myocardial biopsy or intravascular ultrasound, as well as with course and outcomes of the patients. Possible future perspectives that might result are more selective invasive procedures based on imaging results instead of routine schedules, and an early treatment of rejection before global systolic function is affected.

**Segmental left ventricular velocities after transplantation**

In both patient groups (i.e. <12 and >12 months) after Tx, long-axis motion was reduced both in systole and in diastole compared with previously reported segmental velocity data from healthy volunteers [10]. In agreement with our findings, a study based on speckle tracking echocardiography by Saleh et al. [15] reported lower long-axis strains and systolic strain rates in stable Tx patients with normal EF compared with healthy controls. In addition,
previous studies using TDI revealed reduced long-axis velocities in septal and inferior [16] or in lateral regions [17]. However, the TDI studies were limited by incomplete LV coverage or, compared with our results, TDI and speckle tracking-based studies did not provide a complete picture of regional LV function. Using segmental function analysis, we could demonstrate the highest recovery of diastolic long-axis velocities in basal septal and lateral LV regions with increased time after Tx.

Other studies showed that systolic and diastolic long-axis velocities correlated with LV contractility [7] and active relaxation [8]. Persisting segmental long-axis motion abnormalities in stable patients might, therefore, be explained by progressive remodelling going along with fibrosis in the transplanted heart [6]. Furthermore, hearts are only incompletely reinnervated after transplantation [18] and chronic rejection as well as direct effects of immunosuppressive therapy, might lead to a depressed function of the sarcoplasmic reticulum in left ventricular myocardium after Tx and may play a role in the altered myocardial function in these patients [19]. The comprehensive analysis provided by TPM may thus help to monitor the process of remodelling in the Tx heart and to find optimal treatment strategies in order to prevent fibrosis or chronic rejection after Tx.

Influence of time after transplantation

The finding of suppressed systolic and diastolic long-axis function during the first year after Tx, is in line with the literature. Goland et al. [17] reported reduced systolic and early diastolic long-axis velocities soon after Tx, which increased during the first year. These changes go along with an increase in wall thickness during the first 3 months. Moreover, an increase of systolic and diastolic long-axis velocities in the first 6 months after Tx has been described in children [20]. This transient suppression of long-axis velocities might be related to an early ischaemia–reperfusion injury, which is well known to occur after cardiac surgery. Interestingly and in contrast to reduced long-axis velocities, we found increased systolic radial velocities in the first year after Tx. The different behaviours of long-axis and radial velocities might be explained by the predominantly subendocardial location of myocardial fibres with long-axis direction. This predisposes them to ischaemic injury which in the following can induce impaired long-axis function. In contrast, circumferentially orientated fibres underlying radial motion are predominantly situated in the mid-myocardium and might thus have more functional reserves.

Influence of cold ischaemic time

Longer cold ischaemic times were associated with a marked reduction of segmental diastolic long-axis velocities in our cohort. This finding may be supported by evidence that longer cold ischaemic times can result in increased apoptosis of cardiomyocytes, inflammation and mitochondrial injury in the myocardium [21, 22]. The association of a reduction of diastolic function with cold ischaemic time is of particular interest as diastolic dysfunction is proposed as an early indicator of rejection before systolic function is affected in patients after Tx [4]. Whether the diastolic dysfunction due to prolonged cold ischaemic time found in our patient cohort might play a role for the prognosis on the patients with older donor hearts [23] has to be further evaluated.

Ventricular dyssynchrony

We were the first to analyse systolic and diastolic long-axis and radial synchrony in patients after Tx. We found a preserved systolic LV long-axis synchrony in the range of previously published data of healthy volunteers [24]. This is in line with Saleh et al., who also reported a preserved long-axis dyssynchrony in 40 stable patients 1 year after Tx compared with 82 controls. However, Speckle tracking echocardiography was used in this study and dysynchrony based on long-axis strains and strain rates were analysed [15]. In contrast to long-axis dyssynchrony, radial dyssynchrony after Tx was increased (44.8 ± 14.9 compared with 23 ± 4 ms in healthy volunteers [24]). Radial dyssynchrony has been associated with acute rejection in Tx patients [25]. The value of this parameter is further stressed by its significant correlation with LVEF and the lack of correlation with age in our study. Radial dyssynchronous in TX patients was within the range of volunteers (32 ± 14 in Tx vs 27 ± 9 ms in healthy controls), whereas diastolic long-axis synchrony was increased (41 ± 21 vs 22 ± 13 ms) and influenced by donors’ age and time from Tx [24].

Study limitations

Our study is limited by the small number of patients, which does not allow an analysis of multiple subgroups such as different recipient–donor gender constellations, induction therapy or medication. However, a power analysis demonstrated our ability to reliably detect associations between time after transplantation or cold ischaemic time (independent variables) and changes in diastolic LV function (dependent variable). For example, a correlation of cold ischaemic time vs diastolic dyssynchrony can be detected with 90% power, given our sample size (n = 27), our known variances (see Tables 1 and 2) and a minimum effect of 0.22 ms/min. Given that changes in myocardial velocities and cold ischaemic time were much greater than our minimum detectable effect, the ability to find a correlation between diastolic dyssynchrony to cold ischaemic time is feasible.

Furthermore, follow-up studies including the first weeks after transplantation are urgently needed in these patients as many factors influence regional wall motion in the single subject and intra- rather than inter-individual changes need to be evaluated to assess the diagnostic value of regional wall motion abnormalities in TX patients. In these studies, the effect of an induction therapy or other immunosuppressive medication on regional wall motion as well as the combination of biventricular function analysis with tissue characterization has to be further evaluated.

Since biopsy data were available only for 8 patients, the onset of rejection might have influenced the data despite the careful recruitment and clinical assessment of the patients.

Furthermore, the study is limited by the restricted and varying temporal resolution which, though relatively high for an MRI application, is low compared with tissue Doppler or 2D speckle tracking echocardiography and probably resulted in a slight underestimation of peak velocities. In this context, a comparison of myocardial velocities assessed by MRI with values obtained from other modalities such as tissue Doppler echocardiography or Speckle tracking was not performed. Future studies are needed to provide a more detailed comparison between different modalities to improve the understanding of the limitations of each method and the potential differences in myocardial velocity parameters.
CONCLUSIONS

Our results indicated that time after Tx and also cold ischaemic time affected segmental systolic and diastolic motion in patients after Tx. Furthermore, dysynchrony analysis revealed a correlation of diastolic long-axis dysynchrony with the donor’s age and time from Tx. The understanding of these alterations in regional LV motion in the transplanted heart is essential in order to use myocardial velocities as diagnostic tools in transplant rejection or Tx vasculopathy.

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Conflict of interest: none declared.

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