

Title	Four-dimensional flow magnetic resonance imaging assessment of left ventricular hemodynamics in transplanted hearts with good postoperative course		
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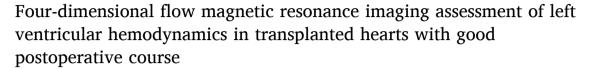
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## Communication





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#### ABSTRACT

Heart transplantation (HTx) is an established treatment for patients with advanced heart failure, although postoperative rejection responses hamper favorable long-term treatment outcomes. Medical imaging is a non-invasive diagnostic modality that can provide attractive insights into cardiac physiology for HTx, including morphological characteristics and cardiac hemodynamics. This study aimed to achieve a basic understanding of left ventricular (LV) hemodynamics in patients with good treatment outcomes following HTx. Specifically, four-dimensional magnetic resonance imaging was performed on 10 patients with a good postoperative course following HTx and 24 controls without a prior history of heart diseases nor HTx. LV hemodynamics were evaluated from the LV flow kinetic energy. We found that LV volumetric functions and kinetic energy ranges were not significantly different between the HTx and control groups, supporting good efficacy of HTx. Nevertheless, a temporal increase in the kinetic energy in late diastole owing to atrial contraction was present in the control group but absent in the HTx group except for one HTx patient. These findings raise the need of further evaluation of cardiac hemodynamics and the pathophysiology of HTx patients even within normal ranges of volumetric and flow transport functions.

#### 1. Introduction

Heart transplantation (HTx) is an established treatment for patients with advanced heart failure [1,2]. Although acute rejection immediately after HTx used to be a critical issue, recent large cohort studies reported that the 5-year survival rate of HTx exceeds 80 % in the United States [3], owing to continuous improvements in pre- and post-transplant management and guideline development [4,5]. Because the majority of patients who undergo HTx are pediatric or young adult populations [2,6], the focus of HTx has been shifted to maintaining favorable long-term treatment outcomes.

Cardiac allograft rejection is inevitable after HTx [7] and manifests as several chronic inflammatory responses. Tissue fibrosis is a common characteristic of remodeling in transplanted hearts [8–12] and is associated with increasing left ventricular (LV) compliance, leading to LV diastolic dysfunction. To detect the symptoms of the rejection response, a clinical guideline recommends that an endomyocardial biopsy [13,14]

is conducted every year after HTx. However, because of the invasiveness of biopsies, medical imaging is an attractive modality for the non-invasive evaluation of transplanted hearts [15–18]. In particular, four-dimensional (4D) flow magnetic resonance imaging (MRI) can provide spatiotemporal hemodynamic profiles [19–22], from which LV dysfunction can be detected, even in subtle or subclinical LV remodeling [23]. Because tissue fibrosis correlates with LV dysfunction, which appears as restrictive cardiac physiology [24] and may alter cardiac hemodynamics in patients with HTx [25], assessment of cardiac hemodynamics would be valuable to deepen our understanding of the cardiac physiology of transplanted hearts and the implications of its alteration.

However, cardiac hemodynamics in patients with HTx has received little attention and has been limited to echocardiographic studies [26–30]. To the best of our knowledge, there have been no 4D flow MRI studies of transplanted hearts in patients with pathological responses or a good postoperative course. According to clinical guidelines, the

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particular cardiovascular physiology of cardiac allografts (e.g., denervation) and surgical complications determine the specific hemodynamics in patients with HTx [31]. On the basis of this consensus, we hypothesized that cardiac hemodynamics in patients with HTx, including patients with HTx and a good postoperative course, would be different from those in healthy controls without a history of heart diseases nor HTx.

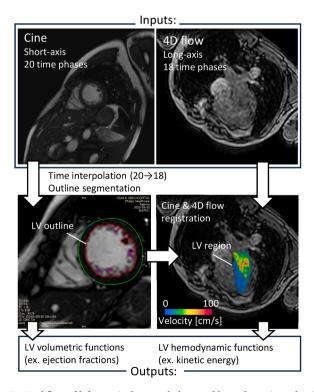
This study aimed to achieve basic knowledge of LV hemodynamics in patients with HTx and a good operative course using 4D flow MRI. Fundamental LV hemodynamics were assessed using established protocols and evaluation indices. The obtained hemodynamic characteristics were compared with those of healthy controls without a prior history of heart diseases nor HTx.

#### 2. Methods

The workflow of the assessment of the LV morphology and hemodynamics in patients with HTx is shown in Fig. 1. This retrospective cross-sectional study was approved by the Institutional Review Boards of The University of Osaka Hospital (No. 20,125–3) and the Graduate School of Engineering Science (No. R3–21), for basic research purposes. The study was performed in accordance with the approved guidelines of the Declaration of Helsinki. Subjects were included after they had provided oral and written informed consent.

We selected 10 patients who underwent HTx by the modified bicaval anastomosis technique [32] and 24 healthy controls. All patients with HTx had no evidence of acute rejection responses in endomyocardial biopsies conducted according to guidelines [14], no abnormal findings in right-heart catheterization, and no symptoms of other diseases. All healthy controls had no prior histories of heart diseases, no medications, and no other abnormalities in health check-ups. MRI scans of patients with HTx were performed in 2020–2022 as an adjunct to a clinical examination. MRI scans of healthy controls were also performed in 2020–2021 using the same scan protocol.

MRI images were acquired in normal sinus rhythm using a 1.5 T Philips Ingenia scanner (version R5.7.1; Philips Healthcare, Best, The



**Fig. 1.** Workflow of left ventricular morphology and hemodynamic evaluation in patients with heart transplantation (HTx) and controls.

Netherlands). 4D flow MRI of each patient was performed with free breathing using an electrocardiogram-triggered, retrospectively navigator-gated, three-dimensional, three-directional, time-resolved, phase contrast MRI sequence (time of repeat, 4.6 ms; echo time, 2.4 ms; flip angle,  $10^\circ$ ; field of view, 320 mm; matrix,  $176\times176\times80$ ; voxel dimensions,  $1.82\times1.82\times1.5$  mm; and 18 time phases in the R-R interval). Velocity encoding of 150 cm/s was set according to [20] for all subjects not to exceed the maximum flow velocity. To obtain LV volumetric data, balanced steady-state free precession cine images were acquired for a stack of short-axis images covering the entire LV and right ventricle (time of repeat, 3.5 ms; echo time, 1.7 ms; flip angle,  $60^\circ$ ; field of view, 320 mm; matrix,  $384\times384\times15$ ; voxel dimensions,  $0.91\times0.91\times10$  mm; and 20 time phases in the R-R interval).

LV regions in 4D flow MRI images were segmented in all time phases by superimposing the short-axis cine MRI images as described previously [33,34]. Original short-axis cardiac magnetic resonance (CMR) images were temporally interpolated from 20 phases to 18 phases using third-order b-spline interpolation, and the LV inner outlines were then extracted using CVI42 (Circle Cardiovascular Imaging Inc., Calgary, Canada). The LV regions were superimposed onto 4D flow MRI images by three-dimensional rigid registration in a representative time phase using Elastix [35]. Registration was restricted to translation only in accordance with a previously reported protocol [33].

To assess LV hemodynamics, flow kinetic energy (KE) and flow transport properties through the LV were analyzed. First, the time course of KE in the LV was computed, as follows.

$$\mathit{KE} = \sum_{i \in \Omega_{LV}} \frac{1}{2} \rho(\mathbf{u}_i \cdot \mathbf{u}_i) \Delta \nu, \tag{1}$$

where  $\rho$  is the blood density (=  $1.05 \times 10^3$  kg/m³),  ${\bf u}$  is the flow velocity vector, and  $\Delta v$  is the volume of each voxel [33,36]. Additionally, KE was normalized by the LV volume in each time phase to remove the effect of an individual LV size, as reported previously [37]. Moreover, flow transport properties based on flow pathlines [34] were analyzed through the LV in a cardiac cycle (please see supplementary 1, and videos 1 and 2 for pathline analyses).

All parameters are shown as the mean  $\pm$  standard deviation (SD) unless otherwise noted. Statistical analyses for correlations between patients with HTx and controls were performed with the two-tailed Mann–Whitney U test using SciPy v1.6.2; (https://scipy.org/)

#### 3. Results

The sociodemographic and physiological parameters of patients with HTx and controls are shown in Tables 1 The LV end-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction (EF) ([EDV–ESV]/EDV) were computed from cine-MRI images. The heart rates of patients with HTx were significantly higher than those of the controls ( $p=1\times10^{-4}$ ), whereas LV EDV, ESV, and the EF were not significantly different between the two groups. Parameters in each patient and controls are shown in Supplementary 2.

Fig. 2 shows the time course of flow KE and normalized KE (by the LV volume) in the LV during the R-R interval in patients with HTx and controls. In all controls, flow KE peaked in systole, early diastole, and late diastole. From the normalized KE, the first, second, and third peaks were extracted in chronological order (Fig. 3). The first peak of flow KE in systole (0.046  $\pm$  0.015 mJ/ml) tended to be similar to the second peak in early diastole (0.042  $\pm$  0.013 mJ/ml), and the third peak in late diastole (0.016  $\pm$  0.008 mJ/ml) was smaller than the other peaks. In patients with HTx, flow KE peaked to 0.040  $\pm$  0.012 mJ/ml in systole and to 0.046  $\pm$  0.012 mJ/ml in early diastole. Moreover, after the second peak, flow KE monotonically decreased from early diastole to the end of diastole, and the third peak was not found, except in one patient (48-year-old man, heart rate = 75 beats/min [bpm], and postoperative period = 1095 days).

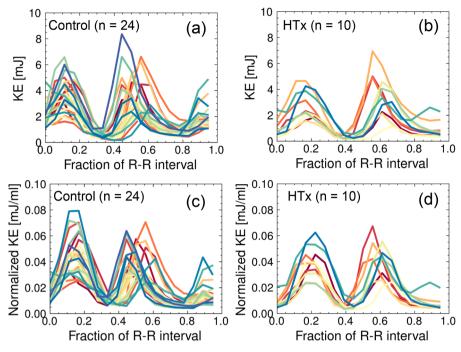


Fig. 2. Time courses of flow KE and normalized KE (by the LV volume) in the LV during the R-R interval in controls (a, c) and patients with HTx (b, d).

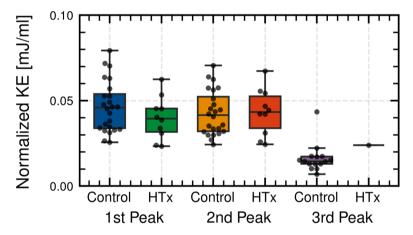


Fig. 3. Box plots of the three local peaks in normalized KE extracted during the R-R interval shown in Fig. 2. Peaks are ordered chronologically.

# 4. Discussion

Compared with the controls, patients with HTx had higher heart rates but similar LV volumes, EFs (Table 1), KE ranges (Fig. 2), and flow components (Supplementary 2). These findings can confirm that the flow transport function of each transplanted heart was successfully

**Table 1** Characteristics of the study population.

	Control $(n = 24)$	$\mathrm{HTx}\;(n=10)$	p-value
Age (y)	45±10	43±9	0.820
Gender (f/m)	7/17	4/6	-
Weight (Kg)	67±10	$59 \pm 11$	0.069
HR at rest (bpm)	63±6	74±5	$1 \times 10^{-4}$
Postoperative period (day)	_	$1152 \pm 514$	_
EDV (ml)	$134{\pm}22$	$120{\pm}28$	0.135
ESV (ml)	51±14	$47 \pm 13$	0.427
Ejection fraction ( %)	62±6	61±5	0.438

HTx: heart transplantation, HR: heart rate, EDV: end-diastolic volume, ESV: end-systolic volume.

restored to the normal range and HTx was efficacious. However, the time course of flow KE was different between patients with HTx and controls (Fig. 3). In patients with HTx, the first and second peaks appeared in systole and early diastole. However, the third peak that appeared in late diastole in controls was absent in patients with HTx except in one patient. Generally, this third peak corresponds to passive LV dilation owing to left atrial (LA) contraction. Although the third peak becomes small with increasing heart rate, the heart rate of the patient with HTx in whom the third peak appeared (75 bpm) was similar to that of the other patients (group mean  $\pm$  SD = 74  $\pm$  5 bpm). Furthermore, there were no characteristic differences in age and postoperative period between this patient and other patients (Table 1). These findings suggest that the loss of the third peak originates in HTx-specific factors.

One possible factor of the loss of third peak, which is commonly understood as the A-wave peak representing atrial contraction, is the progression of LV fibrosis after HTx, increasing elastic compliance [28, 29], and the other factor is LA dysfunction by HTx. Although it is well known that the standard HTx technique (biatrial technique) impairs physiological LA function owing to the formation of mid-atrial anastomoses between the donor heart and the remaining tissues of the

recipient heart, an improved technique (bicaval technique) is considered to preserve physiological morphology and functions [25,31]. However, echocardiographic studies reported that both surgical techniques lead to LA functions that are not significantly different [38], and the bicaval technique decreases LA reservoir functions [39,40]. Furthermore, a recent MRI study showed that LV dysfunction is associated with the geometric relationship between LA and LV [41], even following HTx using the bicaval technique. Further studies on the morphology of the left heart and physiology of transplanted hearts would be valuable for reaching a consensus on the preservation of cardiac physiology by HTx.

This preliminary study has three major limitations. First, the number of patients with HTx is limited because of the difficulty in recruiting a large number of patients with HTx, and additional MRI scans are not included during standard diagnosis. Further investigations with large patient datasets and long-term follow-up of each patient are valuable to clarify the hemodynamic function of transplanted hearts and their association with pathologic progression to achieve favorable long-term outcomes. Second, the MRI scan protocol was selected on the basis of scanner settings and scan time limitations and not optimized for cardiac 4D flow MRI according to the cardiac MRI consensus [19,20]. For example, compared with a relatively large number of time phases, the limited number of time phases of this protocol may result in an underestimated residual volume, affecting flow component analysis [21,42] and making difficult to consider further advanced analyses such as hemodynamic forces [43,44] with higher time resolution. This MRI scan protocol would not affect the main findings of this study because MRI scans of patients with HTx and controls were performed under the same conditions. However, this limitation may prevent the detection of subtle hemodynamic differences between the two groups. Third, although 4D flow MRI is an indispensable tool for the non-invasive evaluation of LV hemodynamics, its inaccessibility is one of the drawbacks for regular long-term evaluation of patients with good treatment outcomes. A more accessible tool such as Doppler echocardiography would be practically useful for further long-term evaluations.

In conclusion, this study is the first to describe LV hemodynamics in patients with HTx using 4D flow MRI assessments. The KE ranges and flow components through the LV were not significantly different between patients with HTx and controls, supporting good treatment efficacy of HTx. However, in patients with HTx, flow KE decreased monotonically from early diastole to the end of diastole, and the local peak in late diastole from atrial contraction was absent, except in one patient. Further studies on cardiovascular hemodynamics and function in patients with HTx are needed to understand the underlying implications of the above findings and the relationship between hemodynamics and the pathophysiology of transplanted hearts.

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# **Competing interests**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential competing interests.

# Ethical approval

Work on human beings that is submitted to *Medical Engineering & Physics* should comply with the principles laid down in the Declaration of Helsinki; Recommendations guiding physicians in biomedical research involving human subjects. Adopted by the 18th World Medical

Assembly, Helsinki, Finland, June 1964, amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975, the 35th World Medical Assembly, Venice, Italy, October 1983, and the 41st World Medical Assembly, Hong Kong, September 1989. You should include information as to whether the work has been approved by the appropriate ethical committees related to the institution(s) in which it was performed and that subjects gave informed consent to the work.

#### Declaration of competing interest

No conflicts of interest

#### Acknowledgments

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.medengphy.2025.104373.

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