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The detection of coronary stiffness in cardiac allografts using MR imaging

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Abstract

Objective—To test the hypothesis that biomechanical changes are quantitatively related to morphological features of coronary arteries in heart transplant (HTx) recipients.

Materials and methods—With IRB approval, three-dimensional (3D) magnetic resonance (MR) angiography and two-dimensional (2D) black-blood steady-state free precession (SSFP) MR imaging were performed to image coronary arteries of 36 HTx patients. Contours of coronary wall were manually drawn. For each coronary segment, coronary wall thickness, wall area, lumen area (in systole and diastole) were acquired. Coronary distensibility index (CDI) and the percent of the coronary wall occupying the vessel area (PWOV) were calculated.

Results—There are totally 98 coronary segments eligible for quantitative analysis from 27 HTx patients. The CDI is $4.90 \pm 2.44 \text{ mmHg}^{-1}$. The mean wall thickness is $1.49 \pm 0.24 \text{ mm}$ and the PWOV is $74.6\% \pm 7.5\%$. CDI has moderate correlations with wall thickness ($r = -0.531$, $P < 0.001$) and with PWOV ($R = -0.435$, $P < 0.001$).

Conclusions—Detected with coronary MR imaging, CDI is quantitatively correlated with the morphological features of the coronary artery in HTx patients. Coronary stiffness has the potential to become an alternative imaging biomarker for the quantitative assessment of the status of cardiac allografts.

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Conflict of Interest One of the authors (XB) is an employee of Siemens health care, R&D, Chicago, Illinois. However, the study is under control of faculty/staff in the Northwestern University. The other authors have no financial disclosure.

Keywords

Heart Transplantation; Magnetic Resonance Imaging; Coronary stiffness

Introduction

Heart transplantation (HTx) is the final live saving resort for treating irreversible heart failure. As a consequence coming with this high cost therapy, cardiac allograft vasculopathy (CAV) greatly affects the prognosis of HTx recipients, especially for those long-term (more than one year) survivals¹. CAV, which is similar to non-transplant coronary artery disease (CAD), has been considered as a chronic inflammatory disease. In clinical practice, CAV is generally diagnosed by detecting diffusely thickened coronary wall in the heart using invasive clinical examinations, such as X-ray angiography and intravascular ultrasound (IVUS)^{2, 3}.

In addition to morphological changes, the biomechanical property of the coronary artery, such as vascular stiffness, has also been reported as a potential quantitative imaging biomarker for the development of CAD in vulnerable populations^{4, 5}. However, the noninvasively measured coronary distensibility and its relations to existing measurements for the evaluation of CAV have never been described in HTx recipients. This knowledge gap exists partly because traditional methods to directly observing both morphological and functional changes on coronary wall are either invasive or requiring X-ray exposure. Furthermore, some special physiological conditions in HTx patients, such as the fast heart rate of denervated donor hearts, adversely affect the performance of noninvasive cardiac imaging techniques. Recently, magnetic resonance (MR) imaging has been introduced as a promising imaging tool for assessing both morphological and biomechanical changes on coronary arteries in various patient groups with repeatability and reproducibility⁴⁻⁷. Therefore, the aim of this pilot study is to test the hypothesis that biomechanical changes are quantitatively related with morphological changes of coronary arteries in cardiac allografts by using a single MR scan.

Materials and methods

Patient study

With approval of institution review board (IRB), 36 HTx recipients (19 Male) were recruited. Written inform consents were obtained from all subjects. No HTx patient had a documented history of kidney insufficiency, acute rejection episode or clinically diagnosed CAV by the time of MR scans. On the examination day, peripheral (brachial) artery blood pressure was taken within 2 hours before or after MR scans to get pulse pressure (PP). For all participants, post-transplantation hypertension was defined as systolic blood pressure (SBP) greater than or equal to 140 mmHg and diastolic blood pressure (DBP) greater than or equal to 90 mmHg, or taking medicine to control arterial blood pressure. Post-transplantation diabetes mellitus was identified by self-reporting or checking the medical record. Clinical CAV was excluded by using one of the criteria listed below: 1) With X-ray angiography, left main artery and primary vessels are in the stage of ISHLT CAV₀, which is

defined as having no detectable angiographic lesion ⁸. 2) With IVUS, there is only minimal (class I) or mild (class II) intimal thickening ⁹. Kidney dysfunction was defined as glomerular filtration rate (GFR) <60%. General information of study subjects is shown in table 1.

MR facility and imaging protocol

All MR scans were performed with a commercial available 1.5 Tesla MR scanner (MAGNETOM, Espree, Siemens healthcare, Germany). A 6-channel phase array coil dedicated for cardiac scan was applied. For each participant, following MR sequences were run within a 75 -minute scan:

Cardiac localization—A 3-plane fast localization sequence was run for anatomic orientation for the coronary tree. The black-blood 2-chamber, 4-chamber and short-axis view were routinely acquired for coronary imaging. The 4-chamber cardiac cine was performed with a segmented 2D steady-state free precession (SSFP) sequence. Imaging parameters included: TR/TE = 2.8/1.1 ms; flip angle = 65°; Spatial resolution = $2.1 \times 2.1 \times 10 \text{ mm}^3$. Totally 22 reconstructive cardiac phases were acquired with retrospective gating. The images of 4-chamber view were used to determine the rest periods of cardiac motion during cardiac cycles.

Whole-heart coronary MR angiography—Whole-heart coronary MR angiography (bright-blood) was acquired with an electrocardiogram (ECG) -triggered, motion adapted navigator (NAV) gated, fat-saturated, T2-prepared, segmented 3D SSFP sequence. Other imaging parameters included: Field of view (FOV) = $320 \times 320 \text{ mm}^2$, TR/TE = 3.7/1.7 ms; flip angle = 90°; K space lines acquired per heartbeat = 17 - 35 (Depending on cardiac motion); readout bandwidth = 870 Hz/pixel; parallel acquisition factor = 2. In-plane spatial resolution was $0.7 \times 0.7 \text{ mm}^2$. Slice thickness 0.7 mm (interpolated from 1.4 mm). In order to measure the coronary distensibility index (CDI), the whole heart coronary MRA was run twice with the same parameters excepting the different acquisition windows. For the first time, acquisition window was located at mid-diastolic period. For the second time, imaging data were acquired in end-systole period ⁵.

Coronary wall MR imaging—Cross-sectional black-blood images of the proximal portions of the coronary arteries was acquired using a NAV gated, ECG-triggered, double inversion recovery (DIR) prepared 2D SSFP sequence ¹⁰. The 3D multiplanar reformations (MPR) were performed on MRA images to localize the left main (LM), the proximal left anterior descending (LAD), and the right coronary artery (RCA). Spectral-selective adiabatic inversion recovery (SPAIR) pulse was used to suppress fat signal and improve contrast between coronary wall and epicardial fat. Imaging parameters included: TR/TE = 4.8/2.4 msec, trigger pulse = 2, FOV = $420 \times 420 \text{ mm}^2$; readout matrix = 448×448 , slice thickness = 4.0 mm. In all cases, the duration of data acquisition will be individually optimized to begin after the onset of the coronary rest period (in mid-diastole) which is determined on the 4-chamber cine images. Being perpendicular to the long axis of vessel, at 5 mm from the origins, three slices in RCA, 1 slice in LM and three slices in LAD were acquired basing on anatomy landmarks ¹¹.

Imaging evaluation and data process

Images were transferred to a dedicated imaging workstation (Dell, Studio XPS 435T, installed with Linux operation system, Ubuntu 11.0) for analysis. The image quality of the 3D whole heart coronary MR angiography and black-blood coronary wall MR imaging was graded with a modified three-point system based on the following criteria by consensus of two authors (KL, with 5 years experience of cardiovascular imaging and YL with 8 years experience of clinical radiology): 1) vessel (lumen) not visible or not eligible for analysis; 2) good image quality, eligible for analysis, vessel (lumen) may have some signal loss or image artifacts; 3) excellent image quality, vessel (lumen) is observed continuously with minor signal loss⁴. Coronary images with a score equal or higher than “2” were enrolled for quantitative analysis.

The images of coronary wall were zoomed to 10 folds (1000%). The outer and inner borders of eligible coronary walls were manually drawn by reader #1 using VesselMASS Software (Leiden University, the Netherlands)^{4, 11}. The area of the vessel wall was defined as the difference between the area of the outer wall and the area of the lumen (outer wall area - luminal area). The mean wall thicknesses were automatically calculated. The percent of the coronary wall occupying the vessel area (PWOV), defined as (vessel wall area / outer wall area) × 100%, was calculated for each coronary wall segment⁴. Cross-sectional images of coronary arteries were reconstructed using MPR based on raw data acquired at the end-systolic and mid-diastolic cardiac cycles. For the images on coronary wall MR imaging and MR angiography (including end-systolic and mid-diastolic), seven transverse views of the RCA, LM and LAD were carefully identified and matched for the same anatomy according to coronary landmarks. The coronary lumens on MR angiography were also zoomed to 10 folds and manually traced^{5, 6}. Lumen areas were automatically calculated according to contours. CDI was calculated based on differences between coronary lumen areas with different acquisition windows. CDI (mmHg⁻¹) was defined as: (Lumen_{systolic} - Lumen_{diastolic}) / (Lumen_{diastolic} × Pulse pressure) × 1000⁵.

Statistical methods

Measurements were expressed in the format of mean ± one standard deviation (SD). Pearson's correlation coefficient (r) was used to investigate correlations between CDI and coronary wall thickness. Bland-Altman plots were used to show the variations of the CDI, wall thickness and PWOV measurements on 10 random selected patients between two independent observers (#1 and #2). All statistical processing was performed with Medcalc software (Version 12.4, Ostend, Belgium). Statistical significance was set at a two-tailed *P*-value <0.05.

Results

Three HTx patients could not tolerate the 75-min MR scan and quit the study. MR scans were completely performed on 33 HTx patients. Both coronary MR angiography and black-blood coronary wall MR imaging were successfully analyzed and measured on 98 coronary segments (39 RCA, 16 LM, and 43 LAD from 27 HTx patients). For coronary segments eligible for quantitative study, the CDI is 4.90 ± 2.44 mmHg⁻¹, the wall thickness is $1.49 \pm$

0.24 mm and the PWOV is $74.6\% \pm 7.5\%$. See table 1. CDI has moderate correlations with wall thickness ($r = -0.531$, $P < 0.001$) and with PWOV ($R = -0.435$, $P < 0.001$). See Figure 1 and Figure 2. Typical images of an HTx patient for the measurements of the LAD are shown in figure 3 a-f.

Low variations of coronary measurements of CDI, wall thickness and PWOV on 32 cross-sectional coronary slices were observed between readers #1 and #2. See figure 4 a-c.

Discussion

By using coronary MR scan, we detected that higher coronary stiffness (lower CDI) are related to thicker coronary wall and higher PWOV in HTx recipients. Such relationships are similar to those findings in older patients with essential hypertension ⁴.

In general non-transplant populations, increased arterial stiffness and vessel wall remodeling, the manifestations of atherosclerosis, are reliable predictors of future clinical cardiovascular events ¹². In Htx recipients, some pathological progressions of vascular lesion after transplantation are similar to atherosclerosis ¹³. Under the unique physiological circumstance of transplant recipients, inflammation (immunological reaction), the ultimate source of almost all pathological changes on vessel wall, is always in a certain active status even under intensive immune suppression. Many humoral and neural mechanisms in HTx recipients may keep contributing to changes on the vessel wall. First, abnormal responsiveness of the renin-angiotensin-aldosterone system (RAAS) to fluid retention exists in HTx recipients ¹⁴. This will ultimately lead to reabsorb more Na^+ and water from the urine. HTx patients appeared to have RAAS that does not appropriately respond to high fluid volume loading. That may lead to overload of both fluid and salt ¹⁵. Second, endothelial cells play a pivotal role in regulating several arterial properties, including vascular tone, vascular permeability, angiogenesis, and the response to inflammation. Endothelial-derived substances, such as NO, endothelin-1, are critical determinants of large arterial compliance, suggesting that endothelial cells may also modulate central arterial stiffness and contribute to post-transplantation hypertension ¹⁶⁻¹⁸. Unfortunately, endothelial cells in cardiac allografts are usually targeted by cellular and humoral reactions between the donor heart and the host ¹⁹. Third, a common used immunosuppressive agent, cyclosporine, may act as another crucial role in HTx patients. Cyclosporine has been implicated in activation of the sympathetic nervous system in HTx recipients, resulting in a higher vascular tone ²⁰.

Comprehensive evaluation of coronary artery is not only important for traditional cardiovascular risk estimation but also potentially meaningful for the status and fate of cardiac allografts. Actually, coronary lesion could be present early after cardiac transplantation even when the coronary wall appears “normal” on traditional X-ray coronary angiography ²¹. Therefore, biomechanical changes of coronary artery were expected to become an early sign of subclinical CAV. Kerber et al imaged 153 coronary segments on 30 HTx patients with IVUS. In 12 patients with early rejection episode, the authors found significantly reduced normalized coronary arterial compliance and increased intimal index (thickness) as compared to those HTx patients without rejection ²². With brachial artery

ultrasound, Roig et al found that impairment of peripheral endothelial-dependent vasodilatation is prevalent soon after HTx (nearly 50% within 1 year of the operation), and low vasodilatation has the potential to predict future CAV, which is well accepted as a special kind of accelerated atherosclerosis and a major contributor for long-term graft failure in HTx patients²³. To the best of our knowledge, the present study is the first attempt to comprehensively obtain both biomechanical and morphological features of coronary arteries in cardiac allografts with a “One-stop-shop” MR scan. Our results suggest that biomechanical features have the potential to serve as quantitative MR imaging biomarkers for the monitoring of the status of the remodeled coronary artery in HTx recipients.

Our study has some limitations. First, we only enrolled stable HTx patients without significant stenosis on coronary artery wall evaluated by IVUS and traditional X-ray angiography, the current clinical “gold standards”. Further studies are highly needed to investigate HTx recipients with diagnosed CAV. Second, we did not compare HTx patients to control subjects for coronary features since these two populations have fundamentally different spectrums of cardiovascular risk factors. Many traditional risk factors for HTx, such as HLA mismatch, donor age, original diseases for HTx, could not be applied to adjust the results of comparison for coronary wall thickness and CDI between HTx patients and healthy controls. For the same reason, we were unable to adjust some potential cardiovascular risk conditions during data analysis, including post-transplantation hypertension and diabetes mellitus²⁴. Third, we did not compare coronary measurements with clinical “gold standards”. Although invasive examinations are routinely performed on HTx patients, some coronary indices, such as CDI, are not regularly available through these regular clinical tests. Fortunately, in previous studies the observed low inter-observer and scan-rescan variability also showed that the gauges of coronary indices were repeatable and reliable^{4, 5, 25}.

Conclusion

Detected with coronary MR imaging, CDI is quantitatively correlated with the morphological features of the coronary artery in HTx patients. Coronary stiffness has the potential to become an alternative imaging biomarker for the quantitative assessment of the status of cardiac allografts.

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Figure 1.

The CDI has a moderate correlation with the wall thickness ($r = -0.531$, $P < 0.001$).

Figure 2.

The CDI has moderate correlation with the PWOV ($R = -0.435$, $P < 0.001$).

Figure 3.

A 54 y/o male had HTx 12 months ago. Heart rate 93 beats /min. Blood pressure: 155/90 mmHg. LAD lumen area is 10.69 mm² in diastole and 12.24 mm² in systole. CDI= $(12.24-10.69)/10.69 \times 1000/65 = 2.23 \text{ mmHg}^{-1}$. The mean wall thickness of LAD measured on black blood image is 1.38 mm. The PWOV is 76.5%.

- a Orientation of coronary artery in systole
- b Orientation of coronary artery in diastole
- c Transverse view of coronary lumen in systole (bright-blood)
- d Transverse view of coronary lumen in diastole (bright-blood)
- e Coronary wall (Black-blood)
- f Tracing and measuring coronary wall thickness

Figure 4.

Inter-observer variations of coronary measurements in HTx recipients

a Bland-alterman plot for coronary wall thickness

b Bland-alterman plot for PWOV

c Bland-alterman plot for CDI

Table 1

Information of the study group.

	HTx patients (N=36)
Age (Years old)	51.4 ± 18.1
Male (%)	19 (53%)
Pulse pressure (mmHg)	59.3 ± 18.1
HTx time (months)	38 ± 19
CDI (mmHg⁻¹)	4.90 ± 2.44
Wall thickness (mm)	1.49 ± 0.24
PWOF (%)	74.6 ± 7.5
HBP (%)	34 (94.4%)
Diabetes (%)	16 (47%)