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Left Ventricular Rotational Mechanics in Children After Heart Transplantation

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Abstract

Background—Left ventricular (LV) dysfunction after orthotopic heart transplantation (OHT) is multifactorial and can be an indicator of graft rejection or coronary artery vasculopathy. Analysis of rotational mechanics may help in the early diagnosis of ventricular dysfunction. Studies describing the left ventricular rotational strain in children after OHT are lacking. It is important to establish the baseline rotational mechanics in pediatric OHT to pursue further studies in this population.

Methods and Results—Rotational strain measured by speckle tracking was compared in 32 children after OHT, with no evidence of active rejection or coronary artery vasculopathy with 35 age-matched normal controls. Twelve OHT patients and 13 controls underwent moderate exercise with pre- and postexercise echocardiography. Torsion, slope of the systolic limb of the torsion–radial displacement loop, and the untwist rate were significantly higher in OHT patients (torsion: median 2.7°/cm [Q1–Q3, 2.3–3.2] versus 2.3°/cm [Q1–Q3, 1.9–2.7]; P=0.03, torsion–radial displacement loop: 2.7°/mm [Q1–Q3, 2.1–3.6] versus 2.0°/mm [Q1–Q3, 1.6–2.7]; P=0.008, indexed peak untwist rate: −21.6°/s/cm [Q1–Q3, −24.3 to −15.7] versus −17.1°/s/cm [Q1–Q3, −19.6 to −13.3]; P=0.01). Contrary to controls, OHT recipients were unable to increase torsion with exercise (OHT: 2.8°/cm [2.7–3.2] versus 3°/cm [2.4–3.5]; P=0.81, controls: 2.2°/cm [2–2.6] versus 3°/cm [2.4–3.7]; P=0.01, pre and post exercise, respectively). The systolic slope of the torsion–radial displacement loop relationship decreased with exercise in most OHT patients.

Conclusions—Baseline rotational strain in OHT patients is higher than normal with a blunted response to exercise. The slope of torsion–radial displacement loop, and its response to exercise, may serve as a marker of left ventricular dysfunction in OHT patients.

Keywords

hemodynamics; mechanics; pediatrics; torsion; transplantation

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Disclosures
None.

The spiral arrangement of the left ventricular (LV) myofibers causes LV torsion during ejection by rotating the cardiac base clockwise and the apex counterclockwise. Torsion aids ejection by wringing blood out of the LV and stores energy within the cardiac matrix. In diastole, the release of stored energy leads to untwisting of the heart. Rapid untwisting leads to creation of an intraventricular pressure gradient in the LV with negative intracavitary pressures at the apex, which in turn produces suction and eventual filling of the LV.[1] The advent of speckle-tracking echocardiography has facilitated the measurement of torsion.[2]

By plotting torsion as an index of force and radial displacement as a surrogate for volume during the same heartbeat, torsion–displacement (Tor-RDi) loops can be generated in a manner reminiscent of pressure–volume loops. A Tor-RDi loop provides coupling of systolic and diastolic contractile events with changes in LV dimensions during a single cardiac cycle. Our previous study in normal children has shown that the systolic limb of the Tor-RDi loop is linear, and its slope becomes significantly steeper with moderate exercise. The loops also become plumper, enclosing larger areas.[3] These facts point to its utility as a useful index of systolic function. Notomi proposed that the area enclosed by Tor-RDi loop may also provide an objective measure of the potential energy stored in the myocardial fibers during systole.[4]

Studies in adults have demonstrated changes in LV torsion during graft rejection and transplant-associated coronary artery vasculopathy.[5–7] However, LV rotational mechanics in children have unique characteristics that are different than adults.[3] Studies evaluating LV rotational mechanics in children after orthotopic heart transplantation (OHT) at baseline and after exercise have not been performed.

The aim of our study was to determine characteristics of LV rotation in children after OHT in the baseline state and after exercise. In adults with diastolic dysfunction in diseases like heart failure with preserved ejection fraction and diabetes mellitus, torsion and untwisting are actually increased.[8,9] After OHT, patients exhibit progressive diastolic dysfunction and chronotropic incompetence.[10] Based on these findings, we hypothesized that baseline rotational indices in OHT patients will be increased, but may show a blunted response to exercise.

Methods

Subject Enrollment

We prospectively enrolled patients at the Children's Hospital of Philadelphia during routine follow up after OHT. The patients included were <21 years old, without evidence of active graft rejection and with no history of coronary artery vasculopathy. The classification system of the International Society for Heart & Lung Transplantation was used to determine presence of graft rejection. Patients were excluded if there was suspicion of graft rejection based on standard clinical findings (changes in LV function, ECG, arrhythmia, valve regurgitation), as well as routine biopsies, obtained yearly. Coronary artery disease was considered absent if the patient's latest coronary angiogram showed no evidence of vasculopathy.

The control group consisted of children with noncardiac chest pain, vasodepressor syncope, and functional heart murmurs and no evidence of anatomic heart disease. Both patients and controls were excluded if ejection fraction was <55% and if there was evidence of systemic hypertension or elevated pulmonary arterial pressure, on the basis of ventricular septal position or a tricuspid regurgitant jet velocity >2.5 m/s. All subjects were in sinus rhythm.

Exercise

Subjects >8 years were asked to perform moderate-intensity exercise. The exercise protocol consisted of repeated straight leg raises to ≈20 inches above the bed, from the hip with full extension of the knee. The goal was to increase the heart rate by 20 to 30 bpm above their baseline. Once the goal was reached, repeat imaging was performed during transient breath holding at end-expiration using the protocol described later. After cessation of exercise, if the heart rate dropped rapidly between apical and basal image acquisitions, the heart rate was titrated by asking patients to perform a few additional leg raises, to maintain the goal heart rate.

Imaging Protocol

To assess LV torsion, parasternal short-axis cine clips of the base of the heart at the level of the mitral valve leaflets and the apex of the heart were obtained. The cardiac apex was defined as the furthest apical extent of the LV cavity, distal to the base of the papillary muscles and just proximal to the level of cavity obliteration. Caution was taken to ensure that the LV shape was circular and not ellipsoid so that the imaging plane was perpendicular to the LV long axis. Three beat clip acquisitions were recorded at a frame rate of >60 Hz. Simultaneous mitral inflow and aortic outflow blood velocities, using spectral pulse Doppler with the sample gate placed just below the LV outflow tract and distal to the anterior mitral leaflet tip, were obtained. These images were used to measure the time of aortic valve closure and mitral valve opening (MVO). The timing of aortic valve closure was considered as 100% of the cardiac cycle. Subjects with heart rate variation between basal and apical acquisition of >5 beats were excluded from the study. All echocardiographic studies were performed on Philips iE33 ultrasound machines (Philips Medical Systems, Andover, MA).

Speckle-Tracking Echocardiography

The Digital Imaging and Communications in Medicine clips of the short axis of the apex and the base of the LV and the apical 4-chamber view were uploaded to a vendor-independent speckle-tracking echocardiography software (2D Cardiac Performance Analysis; TomTec Imaging Systems, Munich, Germany). The endocardial border of the LV was traced. The beginning of tracking was set at the onset of the R wave on EKG. Tracking of the cardiac wall was examined visually on the cine images. Subjects with poor tracking of >1 cardiac segment were excluded. The software generated rotation, rotation rate, radial displacement, circumferential strain, and longitudinal strain data and waveforms.

Construction of Torsion–Radial Displacement Loops

Torsion-indexed radial displacement loops (Tor-RDi) were generated by plotting torsion along the y axis versus indexed radial displacement (RDi) along the x axis (Figure 1C).

Averages of the RDi at the apex and at the base of the heart for every frame were calculated. To account for differences in the size of the LV between children of different ages, the RDi was indexed by dividing it with the LV end-diastolic dimension at the level of the papillary muscles. Patients with discrepancies in the heart rate between the apical and basal acquisitions were excluded by design, and so no correction for heart rate was necessary. The slope of the systolic limb of Tor-RDi relationship was measured. The area enclosed by the Tor-RDi loop was calculated by dividing it into mini trapezoids, each constituting the change in displacement and torsion that occurs in one frame. The area of the loop is the sum of the areas of these trapezoids. This is known as the trapezoidal area of polygon formula and described as follows: sum of $[x(i+1)-x(i)][y(i)+y(i+1))/2]$ for i points of a polygon, where $x(1)$, $y(1)=x(i+1)$, $y(i+1)$.[11] Using preprogrammed formulas inserted into a custom-designed Microsoft Excel sheet, the calculations of the Tor-RDi loop were performed. Inputting the data using cut and paste technique and obtaining the results took ≈5 minutes for each loop.

Definitions

LV rotation and torsion plotted over the course of one cardiac cycle are depicted in Figure 1A. Figure 1B depicts the rotation rates and recoil rates of the apex and base.

From these 2 types of curves, we were able to determine the following:

Systolic Measurements

1. Rotation=Circumferential rotation around the long axis of LV during systole (degree)
2. Twist=apical rotation−basal rotation (degree)
3. Torsion=twist/LV length (degree/cm)
4. Twist slope=slope of the twist–time curve from the lowest twist to peak twist (degree/s)
5. Radial displacement=Movement of endocardium toward the centroid (mm)

Diastolic Measurements—

1. Recoil=the opposite of rotation, returning the myocardium to its starting position (degree)
2. Recoil rate=Velocity at which recoil occurs (degree/s)
3. Untwist slope=the slope of the twist–time curve from peak twist to the inflection point where the steep slope of the curve stops (degree/s)
4. Untwist rate=peak value of apical recoil rate−basal recoil rate (degree/s)
5. Percent untwist at MVO: [(peak twist−twist at MVO)/peak twist]×100. Twist at MVO=(time of MVO−time to peak twist)×untwist rate+y intercept (of untwist rate curve) (%)

To account for differences in LV size between children of different ages, rotation, twist slope, recoil rate, untwist slope, and untwist rate are indexed to LV length at end diastole. Radial displacement is indexed to LV end-diastolic dimension.

The Institutional Review Board of the Children's Hospital of Philadelphia approved the study, and informed consent was obtained from parents and age-appropriate patients.

Statistics

Data are expressed as mean values and standard deviation or median values and first and third quartiles (Q1, Q3) for normally distributed and non-normally distributed variables, respectively. Shapiro–Wilk test was used to determine the distribution of the different variables within the cohort. Student's *t* test and Wilcoxon rank-sum test were used to assess differences between OHT patients and controls at rest for normally distributed and non-normally distributed variables, respectively. Wilcoxon rank-sum test was used to assess differences between OHT patients with and without history of rejection. Wilcoxon signed rank-sum test was used to assess change in variables with exercise. Pearson correlation and linear regression were used to determine covariation between measurements. Intraclass correlation was used to assess intra- and interobserver variability. For all significance testing, a difference was considered significant at P value <0.05. The statistical analysis was performed using Stata (version 13).

For interobserver variability, 15 patients were selected randomly, and the analysis was repeated de novo by 2 blinded investigators. (P. Yubbu and A. Montero). For intraobserver variability, one observer (P. Yubbu) repeated the measurements after 2 weeks.

Results

Study Population Demographics

Forty-two OHT patients and 40 controls were initially included in the study. Ten patients and 5 controls were excluded. One patient showed evidence of rejection on a subsequent biopsy, 4 patients had an ejection fraction of <55%, 2 patients and 3 controls had a heart rate variability of >5 beats between the apical and basal image acquisition, and 3 patients and 2 controls had poor tracking. Our final cohort comprised 32 children with OHT and 35 age- and sex-matched controls. Four OHT patients with right bundle branch block were included in the cohort. None of these patients had right ventricular dysfunction, right ventricular enlargement, or septal shift toward the LV. These 4 patients had major rotational indices similar to the rest of the cohort and subgroup analysis did not reveal any statistically significant differences.

The demographic data and baseline conventional echocardiographic measurements for patients and controls are shown in Table 1. Table 2 summarizes the clinical characteristics of the OHT patients. OHT patients had higher resting heart rate and slightly higher diastolic blood pressure. OHT patients had lower MV e' and a higher E/e' ratio. There was also a trend toward smaller LV dimensions in OHT patients.

Rotational Indices

The results of the rotational indices at baseline are presented in Table 3.

Systolic Measurements

The LV of transplanted hearts in children exhibited higher peak torsion and twist slope during systole than normal LV. There was no difference in the radial displacement between the study groups. Therefore, the transplanted LV underwent more twist per unit change in radial dimensions as shown by higher slope of the Tor-RDi loop during systole.

Diastolic Measurements

In diastole, transplanted hearts exhibited faster untwisting. In both groups, MVO occurred at about the same time during the cardiac cycle, which had been normalized to aortic valve closure time. We did not detect a difference in the amount of untwist that occurs before MVO. In our cohort of OHT patients, the link between systolic twisting and diastolic untwisting was maintained. There was a strong correlation between torsion and untwist rate similar to that in controls (OHT r=0.82, P<0.001, controls r=0.84, P<0.001). The area enclosed by the Tor-RDi loop was not significantly different between OHT and control groups.

Rejection

The baseline characteristics and the rotational indices between patients with and without history of graft rejection are presented in the Tables I and II in the Data Supplement. There were no significant differences in the rotational indices studied between patients with and without history of graft rejection. The overall length of follow-up did not correlate with the magnitude of LV torsion (P=0.55). However, in patients with history of graft rejection, those with longer duration since graft rejection had higher torsion than patients with a more recent rejection episode (r=0.61, P=0.03, r^2=0.38, P=0.03; Figure 2).

Effect of Exercise

Fifteen patients and controls were able to exercise, but only 13 in the control group and 12 in the OHT group had adequate images after exercise to allow for speckle tracking. The results of these 25 subjects before and after exercise are shown in Figures 3–5 and Table 4.

After moderate exercise, both control and the OHT groups increased their heart rates significantly. Controls increased their heart rates more than OHT patients by a small margin (33.2±3.1 bpm versus 25.3±2.1 bpm, respectively, P=0.04). Major differences in myocardial mechanics were detected between the 2 groups during exercise. Patients with OHT showed no change in rotational measurements with exercise apart, from increase in the torsion slope and basal radial displacement. Controls showed an increase in apical rotation, torsion, twist slope, untwist rate, systolic slope of Tor-RDi, and area of Tor-RDi loop. Controls also showed a decrease in basal radial displacement with a decrease in basal circumferential strain after exercise. Basal rotation was unchanged in both groups after exercise.

It is important to note that the inability to increase rotational indices in response to exercise was not universal in all patients with OHT (Figure 4). Four patients with lower Tor-RDi systolic slope at baseline were able to increase their Tor-RDi slope after exercise.

Intraobserver and Interobserver Variability

The intraclass correlations for intraobserver variability for apical rotation and basal rotation were 0.94 and 0.81, respectively. The intraclass correlations for interobserver variability for apical rotation and basal rotation were 0.97 and 0.84, respectively.

Discussion

It is crucial to establish the baseline rotational mechanics in pediatric OHT recipients to pursue further studies in this population. To our knowledge, this is the first study to address this topic in children. Our results indicate that torsion, twist/untwist slopes, peak untwist rate, and the systolic slope of Tor-RDi relationship are all increased in children after OHT. After moderate exercise and modest increases in heart rate by 20 to 30 bpm, the OHT patients were unable to increase their rotational indices. These findings suggest that the reserve to augment rotation and twist in OHT patients after exercise is diminished. The transplanted heart may compensate during exercise by increasing radial displacement at the base.

Our OHT patient population exhibited higher baseline heart rates, slightly higher diastolic blood pressure, lower LV end-diastolic and end-systolic dimensions indexed to body surface area. Their baseline ejection fraction was similar to that of controls. This indicates that these patients were probably functioning at a smaller stroke volume compensated by the higher heart rate. They also had evidence of diastolic dysfunction as indicated by a lower MV e' and a higher E/e' ratio. These findings are consistent with chronic denervation and increased myocardial stiffness that are characteristic of OHT recipients.[10]

Torsion

Our finding of increased torsion is consistent with the hemodynamic state of our patient population. We attribute the increased torsion to the smaller LV end-systolic dimension, diastolic dysfunction, and possible subendocardial dysfunction.[12,13] Mild diastolic dysfunction has been shown to increase torsion in patients with heart failure with preserved ejection fraction.[14] Also, older age is associated with increased torsion, a finding that may be because of subtle subendocardial injury and diastolic dysfunction.[15] Subendocardial dysfunction is an important factor that contributes to increasing torsion. The simultaneous contraction of the subepicardial and subendocardial layers during the ejection phase of systole leads to creation of 2 opposing torques or forces. The subepicardial torque is stronger and dominates the contraction, leading to the counterclockwise rotation of the apex and clockwise rotation of the base. The subendocardial layer at this point is lengthening, and its contraction tries to oppose and balance the dominant subepicardial twisting force. It is the fine-tuning of these 2 forces in relation to the ventricular volume changes during ejection that leads to a uniform transmural myofiber shortening and a decrease in transmural stress that promotes the best energy consumption.[16] In subendocardial dysfunction, the subepicardial force is unbalanced, leading to higher torsion and higher transmural stress for the same amount of volume change. These findings have been documented in patients with aortic stenosis, a disease associated with subendocardial dysfunction.[17] In our study, the systolic slope of the Tor-RDi loop expresses this relation between torsion and ventricular dimensional changes (a surrogate for volume change).

Esch et al[18] compared LV torsion in adults after OHT with 2 groups of controls: a recipient age-matched group and a donor age-matched group. In adults, typically, the donor heart is much younger than the recipient heart. Their OHT patients had similar torsion and response to exercise as recipient age-matched controls (older), rather than donor age-matched controls (younger).[18] Similar biomechanical characteristics are found in patients with type I diabetes mellitus with increased LV torsion related to the duration of diabetes mellitus and load of microvascular disease.[9] These similarities are interesting given that diabetic patients can develop cardiac autonomic neuropathy and predominantly exhibit diastolic dysfunction.

Exercise and Torsion

During exercise, our findings are suggestive of augmentation of cardiac output via increase in heart rate and stroke volume suggested by the increase in basal radial displacement in OHT patients. The increase in stroke volume with exercise in transplanted hearts is caused by early increase in venous return with an increase in LV end-diastolic volume and increase in contractility via the Frank Starling law. This is followed by increase in heart rate as a response to circulating catecholamines.[10] Consequently, one would expect an associated increase in torsion with exercise because of increase in inotropy and LV end-diastolic dimension.[12] However, our results show no significant increase in torsion. Thus, torsion in OHT is dissociated from this increase in stroke volume, in contrast to the response in normal controls. This absence of torsional reserve can lead to higher systolic transmural wall stress and failure to augment diastolic filling during exercise. However, it is important to note that the 4 OHT patients with lower baseline Tor-RDi slopes were able to augment their torsion and Tor-RDi slopes. Therefore, the Tor-RDi slope and the response of the Tor-RDi slope to exercise may serve as a marker differentiating OHT patients without LV dysfunction from those with LV dysfunction.

Untwist Rate

The peak untwist rate in the resting state is faster in OHT patients than in normal children. This is because of higher torsion and storage of energy in the myocardium during systole that is released during early diastole. This may be a compensatory mechanism, whereby, the transplanted heart compensates for a stiffer ventricle and a shortened diastole produced by a higher resting heart rate. The inability to augment torsion and a decrease in the slope of Tor-RDi relationship during exercise may indicate failure of this compensation. The relation of these findings to exercise performance should be the topic of future research.

Torsion–Displacement Loops

We speculate that the Tor-RDi loop may provide insight into the stroke work and stored energy of the LV. The concept is derived from the pressure–volume loop. As LV stroke work increases with exercise, the area enclosed by the pressure–volume loop also increases.[19] We noted a similar phenomenon in our study, when exercise resulted in twist–displacement loops enclosing much larger areas.[3] Notomi et al have also addressed the concept of work. Instead of labeling it as stroke work (a term derived from pressure–volume loops), they coined the term filling work. They speculated that the area enclosed by the loops may indicate the potential energy stored in the myocardial fibers during systole, similar to a wound-up spring. This potential energy is converted into kinetic energy during early diastole, similar to the release of the spring.[4] These concepts are not validated, and further studies are needed to verify them under varying loading conditions and inotropic states.

Clinical Implications

The concept of Tor-RDi loop raised by us may have useful clinical implications. The mathematical calculations for measuring this and other indices proposed by us can be incorporated into calculation packages of commercial echocardiography machines and make online values become available to clinicians. The systolic slope of the Tor-RDi relationship is highly linear and sensitive to inotropic changes. Both these qualities make it an excellent index of systolic function. The peak untwist rate is another useful index that reflects diastolic suction. These computations can be automated in commercial ultrasound machines, which may encourage more clinical use of these indices in diseased states, for example, in cardiomyopathies. We hope that commercial ultrasound companies will pay heed to this type of research and create these automations in future versions of their machines, so that these indices become more prevalent in busy clinical settings.

Limitations

We did not perform a formal cardiopulmonary exercise test; instead, we set a goal of 20 bpm increase in heart rate. This change in heart rate can occur with different levels of exercise in different subjects. Therefore, the patients and controls were probably not exercising at the same level. However, the fact that OHT patients did increase their heart rate and radial displacement with exercise indicates an adequate effort.

We used a vendor-independent software (TomTec) to assess rotational indices. A potential advantage is that it allows the analysis of data from different echocardiography machines that would be especially important in multicenter research protocols. For detecting acute graft rejection, a single center’s sample size may not be sufficient and multicenter studies may be needed. Longitudinal strain values can be measured reliably from stored Digital Imaging and Communications in Medicine images at a compressed frame rate of 30 frames/second and agree well with strain values obtained at 60 frames/second.[20] However, there are no studies to date that have compared rotational indices derived from vendor-independent and vendor-specific software. The lower frame rate of Digital Imaging and Communications in Medicine images used by TomTec may potentially have limited our ability to capture the true peak values for rotational measurements that occur during phases of the cardiac cycle that are brief, for example, peak untwist rate during isovolumic relaxation. However, we speculate that this phenomenon may potentially affect both the study group and the control group. Moreover, the lower frame rate should not affect the Tor-RDi slope or the twist and untwist slopes, given the linear relation and multiple data points available to draw these slopes even with the lower frame rate.

Conclusions

Children after OHT have higher baseline torsion, twist/untwist slopes, peak untwist rate, and torsion to radial displacement slope. Children after OHT do not augment their rotational strain with exercise. Our study also addresses a newer concept demonstrating differences in the response of the slope of Tor-RDi systolic relationship to exercise that may be used as an early marker of LV dysfunction. Further studies in OHT patients using rotational strain should take into account the baseline characteristics of the OHT population rather than comparing them to normal controls.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CLINICAL PERSPECTIVE

This study shows significant differences in rotational strain parameters between orthotopic heart transplant recipient children and controls during baseline rest and after exercise. Torsion, twist/untwist slopes, untwist rate, and the systolic slope of torsion to radial displacement relationship are all increased in children after orthotopic heart transplant. After moderate exercise, orthotopic heart transplant patients are unable to increase any of their rotational indices unlike controls. However, these differences are not universal among all patients after orthotopic heart transplant. Patients with lower torsion to radial displacement relationship slope at rest were able to increase that slope after exercise. The concept of the torsion to radial displacement relationship loop may have useful clinical implications. The systolic slope of the torsion to radial displacement relationship is linear and sensitive to inotropic changes. Both these qualities make it an excellent candidate as an index of systolic function. The untwist rate is another useful index that reflects early diastolic suction. We speculate that the presence of abnormalities in these indices may be used to detect subtle left ventricular dysfunction. How these abnormal values of rotational parameters relate to prognosis, exercise performance, and quality of life should be the aim of future research. Also, studies addressing rotational strain during acute rejection or coronary artery vasculopathy should take into account the baseline characteristics in this population rather than comparing them to normal controls. These computations can be automated in commercial ultrasound machines, which may encourage more clinical use of these indices in diseased states, for example, in cardiomyopathies.

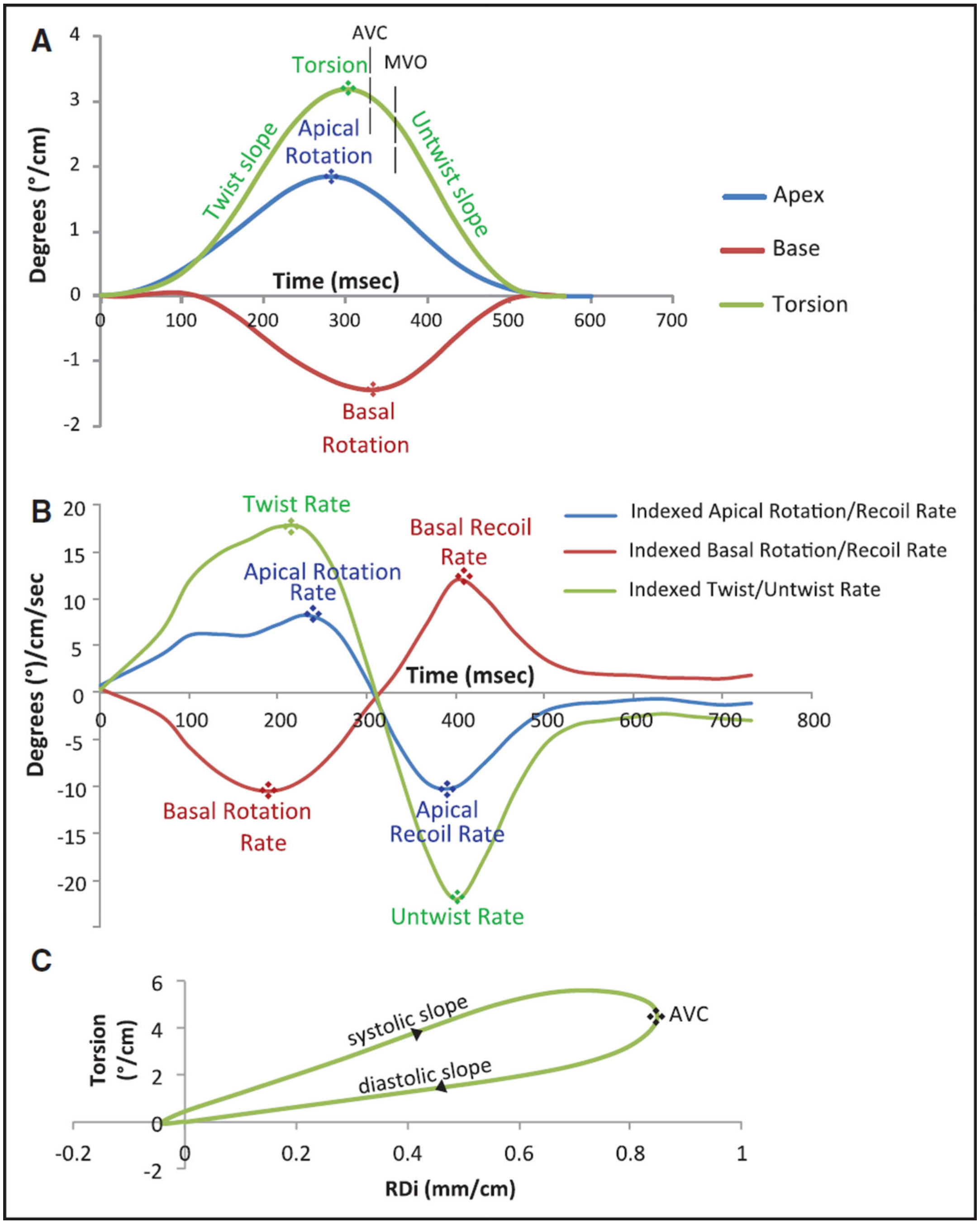

Figure 1.

Images depicting various left ventricular (LV) rotational measurements. **A**, Plot of apical (blue) and basal (red) rotations and twist (green) in degrees/cm during the cardiac cycle. **B**, Plot of apical, basal rotations, and twist rates in systole. Recoil and untwist rates in diastole are also depicted in the same figure. **C**, Plot of torsion–radial displacement (indexed) loop. The systolic limb of this loop is linear. AVC indicates aortic valve closure; MVO, mitral valve opening; and RDi, radial displacement indexed to LV end-diastolic dimension.

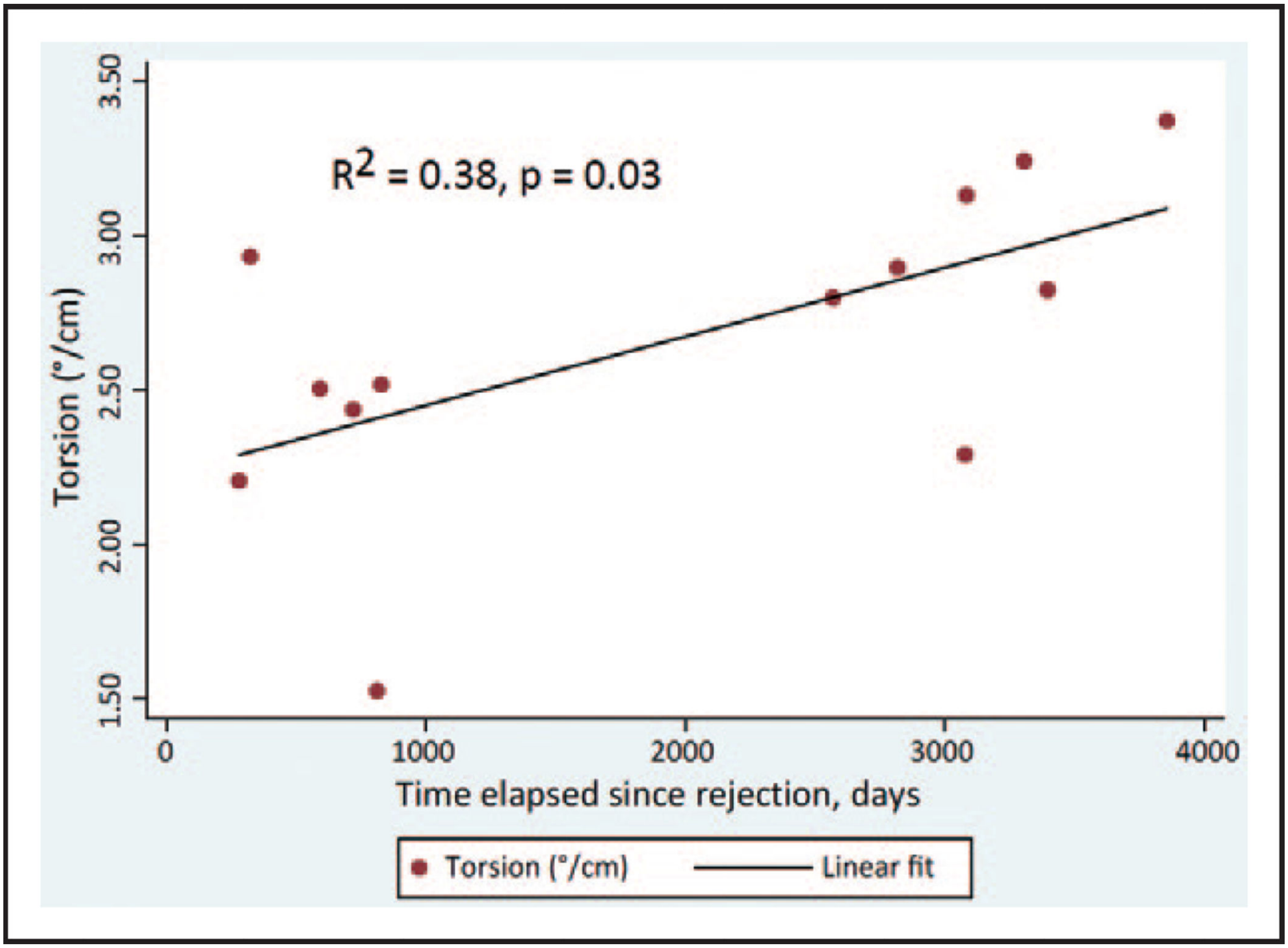

Figure 2.

Scatterplot depicting enhancement in left ventricular (LV) torsion after a longer period has elapsed in orthotopic heart transplantation (OHT) patients since their last episode of rejection.

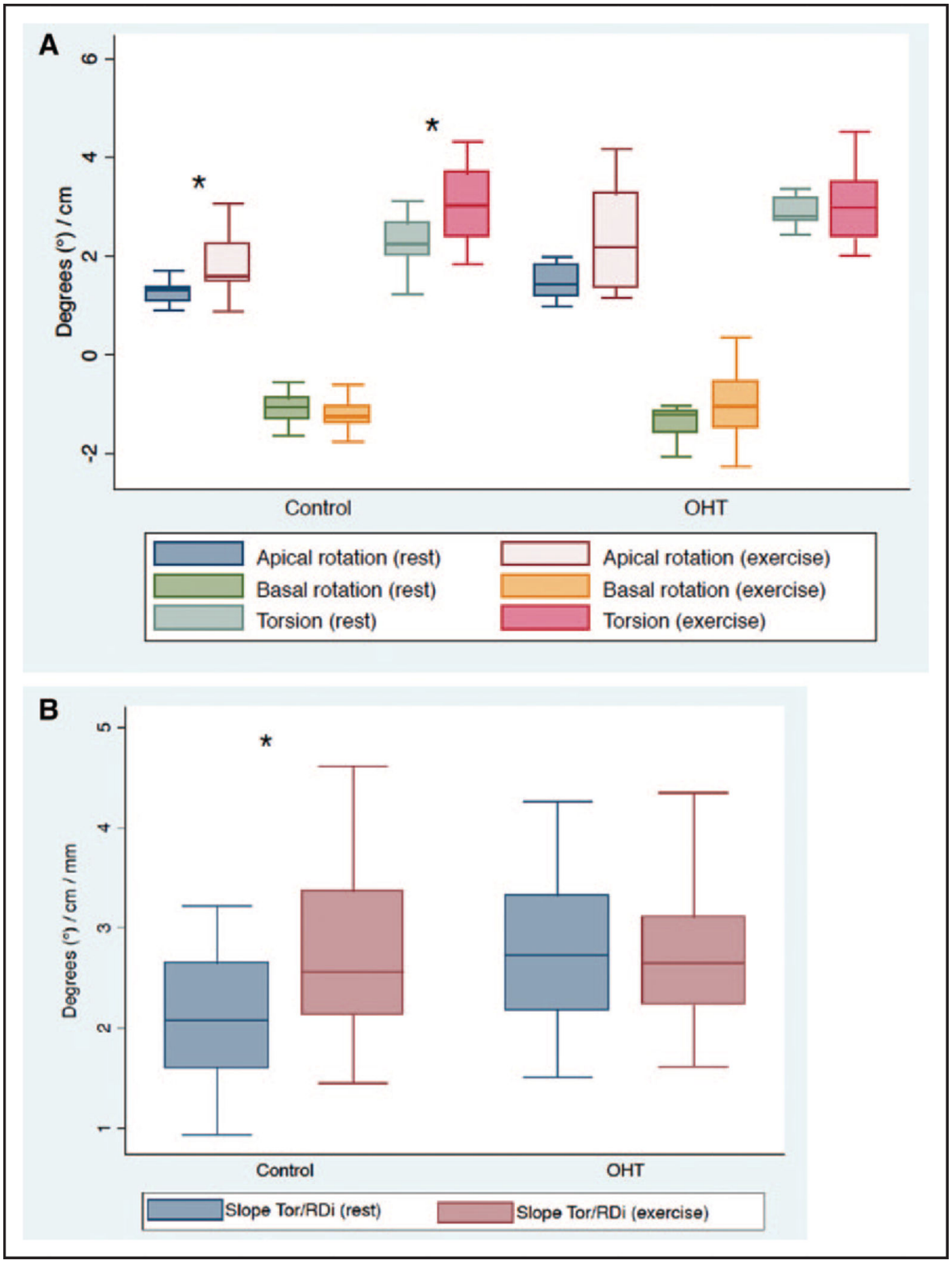

Figure 3.

Box plots depicting changes with exercise in (**A**) apical rotation, basal rotation, and torsion and (**B**) slope of the systolic limb of the torsion–radial displacement loop. The boxes represent the interquartile range, the line within the box represent the median, and the whiskers represent the minimum and maximum values. **P* value <0.05 between rest and exercise. OHT indicates orthotopic heart transplantation; and slope Tor-RDi, systolic slope of the torsion–radial displacement loop.

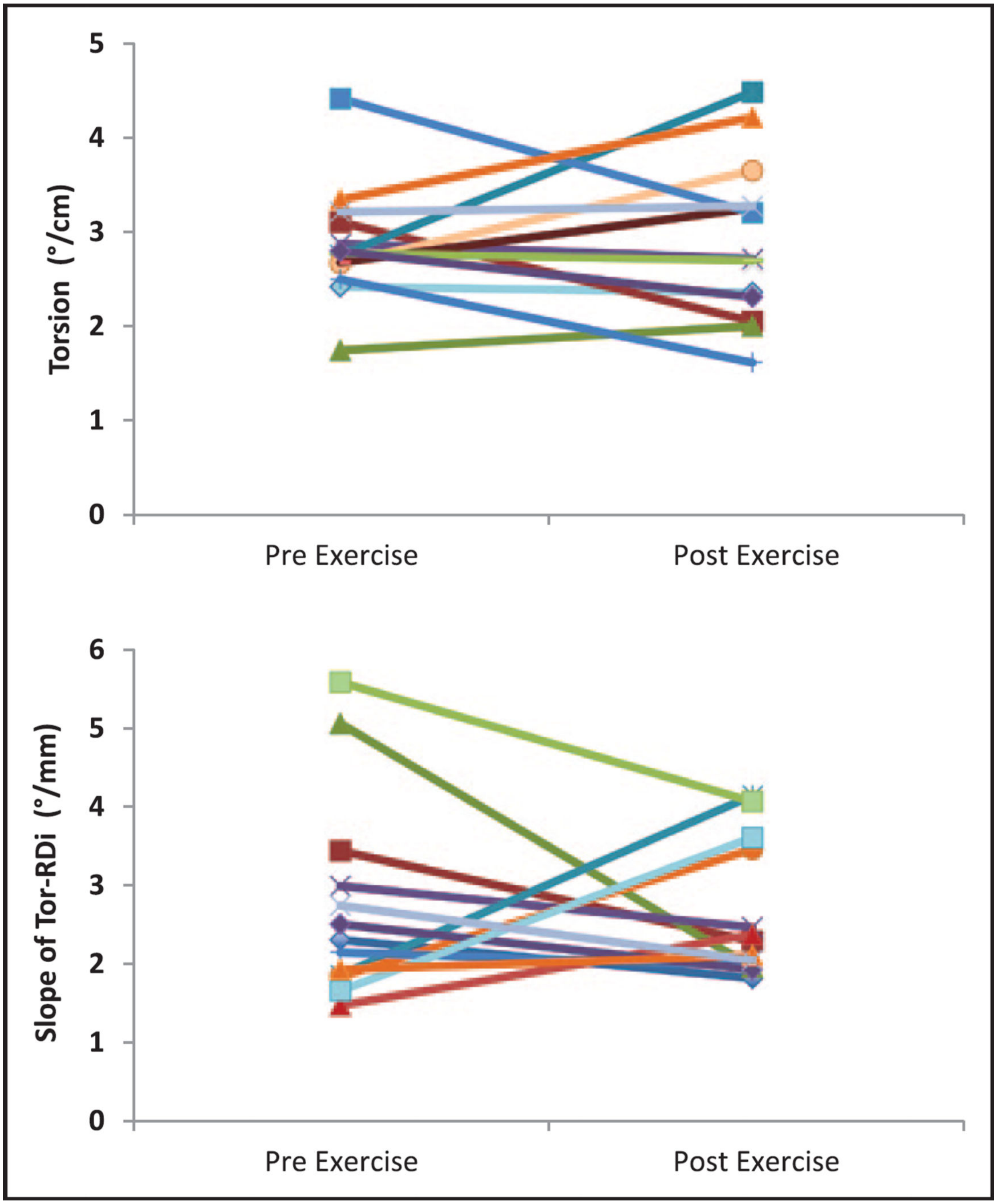

Figure 4.

Line graph depicting left ventricular (LV) torsion and slope of Tor-RDi relationship in orthotopic heart transplantation (OHT) patients pre and post exercise. Overall patients with OHT showed no significant change in torsion and slope of Tor-RDi relationship with exercise. The inability to increase rotational indices in response to exercise was not universal in all patients with OHT. Patients, who started with low Tor-RDi slope at rest, were able to increase their Tor-RDi slopes after exercise. However, in OHT patients who started with higher resting Tor-RDi slope, the slope decreased. OHT indicates orthotopic heart transplantation; and Tor-RDi, torsion–radial displacement loop.

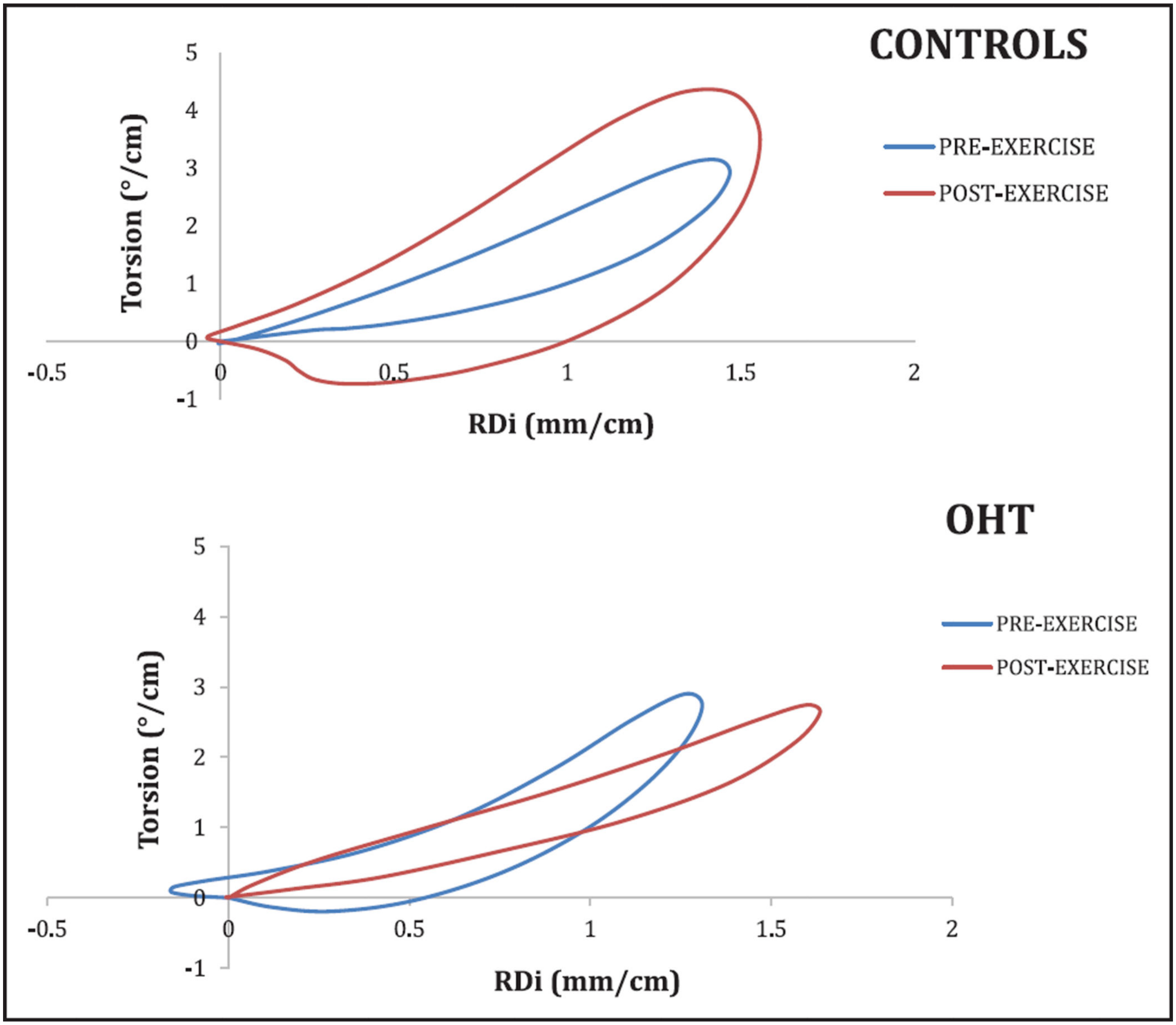

Figure 5.

Torsion-RDi loops of controls and orthotopic heart transplantation (OHT) patients pre and post exercise. With exercise, these loops enclosed a larger area, and the slope of the systolic limb became steeper in contrsol patients, but not in OHT patients.

Table 1

Demographic Characteristics and Conventional Echocardiographic Measurements in Transplant Patients and Controls

Variable	OHT (n=32)	Controls (n=35)	*P* Value
Age, y	12.6 (8.3, 15.6)	10.9 (7.3, 13.4)	0.15
Female, %	56.3	48.6	0.53
BMI	18.3 (15.9, 22.7)	18.9 (15.8, 20.8)	0.78
BSA, m^2	1.28 (0.96, 1.65)	1.28 (0.85, 1.59)	0.76
Heart rate, bpm	96.1±17	79.5±21	<0.001 *
Systolic BP, mm Hg	109.9±11.5	106.5±14	0.31
Diastolic BP, mm Hg	66.3±8.9	61±7.9	0.02 *
LVEDD, cm	3.8±0.6	4.1±0.8	0.11
LVEDDi, cm/m^2	3.1 (2.6, 3.8)	3.5 (3, 4.4)	0.06
LVESD, cm	2.4±0.5	2.6±0.5	0.2
LVESDi, cm/m^2	2 (1.7, 2.4)	2.2 (1.9, 2.8)	0.05
Ejection fraction, %	66.3±6.5	65.5±5.5	0.58
E, m/s	0.9 (0.66, 1.11)	0.93 (0.78, 1.03)	0.85
Lateral mitral e', m/s	0.1 (0.08, 0.13)	0.14 (0.12, 0.15)	<0.001 *
Lateral mitral E/e'	9.5 (6.7, 11)	6.8 (5, 8.4)	0.003 *
LV longitudinal strain, %	−19.9±4.5	−19.9±3.4	0.96

Data presented as mean±standard deviation or median (first and third quartiles) for normal and non-normal distribution, respectively. BMI indicates body mass index; BP, blood pressure; BSA, body surface area; *E*, early peak velocity of mitral valve inflow Doppler; e', early diastolic peak velocity of the mitral valve lateral annulus by tissue Doppler; LV, left ventricle; LVEDD(i), LV end-diastolic dimension indexed to BSA; LVESD(i), LV end-systolic dimension indexed to BSA; and OHT, orthotopic heart transplantation.

* $P<0.05$.

Table 2

Transplant Patients Clinical Characteristics

OHT Patient Characteristics (n=32)	
Underlying diagnosis	
Congenital heart disease	10 (31%)
Cardiomyopathy	22 (69%)
Graft health	
Age of graft in months	52 (21, 121)
Chronic rejection	0 (100%)
Ever rejection	12 (27%)
Time from prior rejection to echo	91 (28, 108)
Cardiac allograft vasculopathy (CAV)	0 (0%)
Co-morbidities	
Known mild renal injury	9 (28%)
Other organ transplant	2 (6%)
Resolved PTLD	4 (13%)
Highest grade rejection on biopsies within 1 y of analyzed echo	
0R	23 (72%)
1R	9 (28%)
2R–3R	0 (0%)
pAMR0	31 (97%)
pAMR1	1 (3%)
pAMR2–3	0 (0%)
Time interval from analyzed echo	
Biopsies before echo	6 (3, 8)
Biopsies after echo	4 (2, 6)
Angiography before echo	7 (3, 9)
Angiography after echo	4 (2, 6)
Had biopsies within 6 mo of echo	32 (100%)
Had angiography within 6 mo of echo	30 (94%)
Immunosuppressant medications	
Mycophenolate	21 (66%)
Azathioprine	9 (28%)
Tacrolimus	25 (78%)
Sirolimus	10 (31%)
Steroid	1 (3%)
Number of medications	
1	1 (3%)
2	28 (87.5%)
3	3 (9.5%)

All variables above are listed as median (first and third quartiles) or as number (%) except for times, which are expressed in months. OHT indicates orthotopic heart transplantation; pAMR, pathological antibody mediated rejection; and PTLD, post-transplant lymphoproliferative disorder.

Table 3

Left Ventricular Rotational Indices in Transplant Patients and Controls

Variable	All OHT Patients (32)	Controls (35)	*P* Value
Apical rotation (i), degree	1.4 (1.2, 2)	1.3 (1.0, 1.5)	0.07
Basal rotation (i), degree	−1.2 (−1.6, −1.0)	−1.1 (−1.6, −0.9)	0.37
Torsion, degree/cm	2.7 (2.3, 3.2)	2.3 (1.9, 2.7)	0.03 *
Torsion slope (i), degree/s/cm	10.9 (9, 15.5)	9.9 (7.9, 12.6)	0.05
Percent untwist at MVO, %	45±16	54±24	0.08
Untwist slope (i), degree/s/cm	14 (8.8, 16.7)	11.6 (7.5, 13)	0.05
Untwist rate (i), degree/s/cm	−21.6 (−24.3, −15.7)	−17.1 (−19.6, −13.3)	0.01 *
Peak RDi apex, mm/cm	1.09 (0.88, 1.32)	1.12 (0.92, 1.24)	0.9
Peak RDi base, mm/cm	1.17 (0.9, 1.45)	1.28 (1.16, 1.42)	0.15
Systolic slope of Tor-RDi loop, degree/mm	2.7 (2.1, 3.6)	2.0 (1.6,2.7)	0.008 *
Tor-RDi loop area, degree .mm/cm^2	0.6 (0.3, 0.84)	0.52 (0.29, 0.78)	0.48
Circumferential strain–apex	−31.5 (−35.7, −26.4)	−30.1 (−32.6, −26.7)	0.41
Circumferential strain–base	−21.6 (−25.6, −18.0)	−23.3 (−26.5, −21.1)	0.12

(i) indicates indexed to LV length; LV, left ventricle; MVO, mitral valve opening; OHT, orthotopic heart transplantation; RDi, radial displacement indexed to LV end-diastolic dimension.

* $P<0.05$.

Table 4

Left Ventricular Rotational Indices in Transplant Patients and Controls Before and After Exercise

Variable	OHT Rest[12]	OHT Exercise[12]	*P* Value OHT: Rest vs Exercise	Controls Rest[13]	Controls Exercise[13]	*P* Value Controls: Rest vs Exercise	*P* Value Controls vs OHT Exercise
Heart rate	96.3±16.6	121.5±20.2	0.002*	71.5±12.8	106.2±20.8	0.002*	0.04*
Apical rotation (i), degree	1.4 (1.2, 1.8)	2.2 (1.3, 3.2)	0.07	1.3 (1.1, 1.4)	1.6 (1.5, 2.3)	0.01*	0.33
Basal rotation (i), degree	−1.2 (−1.6, −1.1)	−1.0 (−1.5, −0.5)	0.21	−1.1 (−1.3, −0.9)	−1.2 (−1.4, −1.1)	0.11	0.38
Torsion, degree/cm	2.8 (2.7, 3.2)	3.0 (2.4, 3.5)	0.81	2.2 (2.0, 2.6)	3.0 (2.4, 3.7)	0.01*	0.79
Torsion slope (i), degree/s/cm	13.0 (9.3, 15.8)	16.6 (11.8, 17.7)	0.04*	9.8 (8.2, 10.8)	13.7 (10.8, 16.9)	0.01*	0.48
Untwist slope (i), degree/s/cm	15.9 (11.7, 16.7)	15.4 (11.2, 18.8)	0.58	11.3 (8.3, 12.5)	12.9 (8.7, 17.7)	0.07	0.72
Untwist rate (i), degree/s/cm	−21.9 (−26.3, −15.9)	−20.9 (−29.7, −17.4)	0.48	−15 (−18.8, −12.4)	−23.5 (−29.7, −15.2)	0.01*	0.96
Peak RDi apex, mm/cm	1.2 (0.8, 1.5)	1.3 (0.9, 1.5)	0.48	1.1 (0.9, 1.2)	1.1 (0.9, 1.3)	0.31	0.45
Peak RDi base, mm/cm	1.2 (1.0, 1.3)	1.4 (1.2, 1.6)	0.03*	1.3 (1.2, 1.4)	1.1 (1.1, 1.3)	0.02*	0.02*
Systolic slope of Tor-RDi loop, degree/mm	2.7 (2.2, 3.3)	2.4 (2, 3.6)	0.53	2.1 (1.6, 2.7)	2.6 (2.1, 3.4)	0.04*	0.83
Tor-RDi loop area, degree mm/cm^2	0.54 (0.28, 0.94)	0.44 (0.32, 0.97)	0.81	0.45 (0.26, 0.6)	0.79 (0.25, 1.43)	0.04*	0.45
Circumferential strain–apex, %	−33.7 (−39.1, −30.8)	−32.3 (−42.3, −25.0)	0.64	−30.7 (−36.8, −26.1)	−36.9 (−40.8, −25.5)	0.17	0.71
Circumferential strain–base	−21.6 (−24.8, −18.6)	−25.1 (−28.8, −20.8)	0.07	−24.2 (−27.3, −21.7)	−23.3 (−24.2, −21.4)	0.03*	0.23

(i) indicates indexed to LV length; OHT, orthotopic heart transplantation; RDi, radial displacement indexed to LV end diastolic dimension.

* $P<0.05$.