Impaired Right Ventricular Function in Heart Transplant Rejection

Luciana J. B. M. Carrion,[1] Alice Sperotto,[2] Raffaela Nazario,[1,2] Livia A. Goldraich,[2] Nadine Clausell,[1,2] Luís Eduardo Rohde,[1,2] Angela Barreto Santiago Santos[1,2]

Universidade Federal do Rio Grande do Sul - PPG em Cardiologia,[1] Porto Alegre, RS – Brazil

Hospital de Clínicas de Porto Alegre – Cardiologia,[2] Porto Alegre, RS – Brazil

Abstract

Background: The practice of screening for complications has provided high survival rates among heart transplantation (HTx) recipients.

Objectives: Our aim was to assess whether changes in left ventricular (LV) and right ventricular (RV) global longitudinal strain (GLS) are associated with cellular rejection.

Methods: Patients who underwent HTx in a single center (2015 – 2016; n = 19) were included in this retrospective analysis. A total of 170 biopsies and corresponding echocardiograms were evaluated. Comparisons were made among biopsy/echocardiogram pairs with no or mild (0R/1R) evidence of cellular rejection (n = 130 and n = 25, respectively) and those with moderate (2R) rejection episodes (n=15). P-values < 0.05 were considered statistically significant

Results: Most patients were women (58%) with 48 ± 12.4 years of age. Compared with echocardiograms from patients with 0R/1R rejection, those of patients with 2R biopsies showed greater LV posterior wall thickness, E/e' ratio, and E/A ratio compared to the other group. LV systolic function did not differ between groups. On the other hand, RV systolic function was more reduced in the 2R group than in the other group, when evaluated by TAPSE, S wave, and RV fractional area change (all p < 0.05). Furthermore, RV GLS (−23.0 ± 4.4% in the 0R/1R group vs. −20.6 ± 4.9% in the 2R group, p = 0.038) was more reduced in the 2R group than in the 0R/1R group.

Conclusion: In HTx recipients, moderate acute cellular rejection is associated with RV systolic dysfunction as evaluated by RV strain, as well as by conventional echocardiographic parameters. Several echocardiographic parameters may be used to screen for cellular rejection. (Arq Bras Cardiol. 2020; 114(4):638-644)

Keywords: Ventricular Dysfunction, Right; Heart Transplantation; Graft Rejection; Echocardiography/methods; Strain; Speckle Tracking.

Introduction

Over the last five decades, heart transplantation (HTx) has become an established therapeutic option for patients with end-stage heart failure.[1,2] Improvements in surgical techniques, patient selection, immunosuppressive drugs, and post-HTx protocols have contributed to the success of this therapy and increased patient survival.[2-5]

Post-HTx follow-up is focused on active screening for complications. Periodic endomyocardial biopsies can diagnose most cases of acute cellular rejection (ACR), in which patients are mostly asymptomatic, and left ventricular ejection fraction (LVEF) remains normal.[2,6] However, endomyocardial biopsy is an invasive and costly procedure with potentially serious complications.[2,7-9] The search for other methods that can screen for rejection is thus becoming increasingly important.

A few studies on novel echocardiographic techniques, such as two-dimensional speckle-tracking echocardiography (2D STE), have shown that reduction of left ventricular (LV) global longitudinal strain (GLS) is associated with graft rejection, and it can be used to detect early subclinical myocardial dysfunction. However, there is no consensus in the literature in relation to the clinical applicability of GLS assessment in this scenario.[2-6,10] Furthermore, little is known about right ventricular (RV) GLS and its potential role in rejection, highlighting the research gaps in this area.[10-12]

Seeking to expand current knowledge about early myocardial dysfunction and graft rejection, the present study was designed to evaluate whether changes in myocardial strain by speckle tracking are associated with ACR. Specifically, we aimed to evaluate whether reduced LV GLS and RV GLS are associated with cardiac graft rejection.

Methods

Study Population

All adult patients (age > 18 years) who underwent HTx at the Hospital de Clínicas in Porto Alegre, Rio Grande do Sul, Brazil, between 2015 and 2016 were included in this analysis. During this period, patients received routine

Mailing Address: Angela Barreto Santiago Santos •
Hospital de Clinicas de Porto Alegre – Cardiologia - Rua Ramiro Barcelos, 2350, Sala 2061. Postal Code 90035-903, Porto Alegre, RS – Brazil
E-mail: abssantos@hcpa.edu.br
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monitoring per hospital protocol, and their data were analyzed during the first 18 months of follow-up after HTx. Of the 20 patients who received transplants (all via the bicaval technique), 19 were included in this analysis, and one patient who died before the first endomyocardial biopsy due to hyperacute graft rejection was excluded. The standard institutional follow-up protocol, which served as a guide for this study, consisted of weekly biopsies in the first month post-HTx; biopsies every other week during the second and third months post-HTx; monthly biopsies from the fourth to the sixth month post-HTx; and subsequent biopsies every three to four months until 18 months of follow-up had been completed. Each biopsy was followed by echocardiography, seeking to detect post-biopsy complications.

Of the 257 biopsies performed up to July 2017, 170 had corresponding echocardiograms with images suitable for strain analysis by the speckle-tracking method and were thus included in this study (Figure 1). Comparisons were made among biopsy/echocardiogram pairs with no (0R) or mild (1R) evidence of rejection (n = 130 and n = 25, respectively) and those with moderate (2R) rejection episodes (n = 15). This study was conducted in accordance with the standards set out in the Declaration of Helsinki, and its protocol was approved by the institutional Research Ethics Committee.

Echocardiographic Analysis

All echocardiograms were recorded and analyzed offline on a TOMTEC workstation (TomTec Imaging Systems, Unterschleißheim, Germany) by an experienced echocardiographer (LJBMC) blinded to clinical data and to the corresponding biopsies. Measurements were obtained according to American Society of Echocardiography (ASE) standards, including septal and posterior wall thicknesses; diameters of the LV, RV, aorta, and left atrium; transmitral flow; mitral and tricuspid annular relaxation velocities; and tricuspid annular excursion.

Echocardiographic measures of RV function were performed using the apical 4-chamber view. Tricuspid annular plane systolic excursion (TAPSE) was measured as the vertical displacement of the tricuspid annulus from end-diastole to end-systole using M-mode. The tissue Doppler-derived tricuspid lateral annular systolic velocity wave (S wave) was obtained aligning the basal segment and the tricuspid annulus with the Doppler cursor. RV fractional area change (FAC) was evaluated by manual tracing of RV areas as follows: (RV end-diastolic area − RV end-systolic area) / RV end-diastolic area × 100.

Analysis of myocardial deformation (GLS) was performed using specific B-mode speckle-tracking software for the LV and the RV (2D CPA TTA2.20.01, TomTec). This software circumvents angle dependency and identifies cardiac motion by tracking multiple reference points over time. At end-systole, as defined by ECG, three landmarks were established at the endocardial edge (two basal and one apical), with automatic detection of speckles along the endocardial edge of the specified cavity (LV or RV). Manual adjustments were made when necessary. In the LV, peak-systolic strain for each 2D apical view (two-, three-, and four-chamber) was automatically obtained from the mean of the 6 traced segments, while LV GLS was obtained by averaging the peak-systolic strain of apical views. In the RV, RV GLS was defined as the peak-systolic strain that combined the free wall and the septum (Figure 2). All patients were in sinus rhythm, and a single cardiac cycle was analyzed. Images in which poor quality precluded speckle analysis in two or more consecutive segments, images covering less than one complete cardiac cycle, or excessively tangential views were excluded. LV and RV end-systolic and end-diastolic volumes were used to derive other measures of myocardial function, such as LVEF (by the modified Simpson method) and RV FAC.

Intraobserver variability for LV GLS and RV GLS was assessed in a sample of 20 randomly selected echocardiograms. The coefficient of variation was 3.8% and 6.7% for LV GLS and RV GLS, respectively. Intraclass correlation coefficients were 0.96 for LV GLS (95% confidence interval: 0.91 – 1.0) and 0.80 for RV GLS (95% confidence interval: 0.59 – 1.0).

Endomyocardial Biopsy

Endomyocardial biopsies were scheduled as required by the standard institutional protocol. All were performed through an internal jugular vein access, at the catheterization laboratory. During the procedure, a sheath was advanced to the interventricular septum through the tricuspid valve, and 3 – 6 small fragments were retrieved with a cardiac bioptome for histological analysis. Tissue samples were evaluated by a single experienced pathologist who was blinded to the results of the echocardiographic studies. Biopsies were examined for ACR, graded on a scale from 0R to 3R, according to the International Society for Heart and Lung Transplantation (ISHLT) classification.[13] All patients with biopsies classified as ≥ 2R were treated with a standard regimen for rejection, while those with biopsies classified as 1R were monitored closely and remained on maintenance immunosuppression therapy, following institutional protocols.

Statistical Analysis

Normally distributed continuous data were expressed as means and standard deviations, and categorical data were shown as absolute and relative frequencies. Echocardiography variables were compared using ANOVA adjusted for each HTx patient accounting for repeated measurements. All statistical analyses were performed in the SPSS software package. All tests were two-sided, and p-values < 0.05 were considered statistically significant.

Results

Most HTx recipients (n = 19) followed in this study were women (n = 11; 58%), with a mean age of 48 ± 12.4 years. In general, few had other comorbidities, and the main etiology of heart failure was of non-ischemic origin. Donors were mostly young men, with a mean age of 29 years (Table 1).

Of the 257 biopsies performed in this period, the results of 66% (n = 170) correlated with echocardiography. Of the biopsies excluded from analysis (87 without corresponding echocardiograms), 24 showed 1R rejection; two showed 2R rejection; and one showed 3R rejection. Of the 170 biopsies

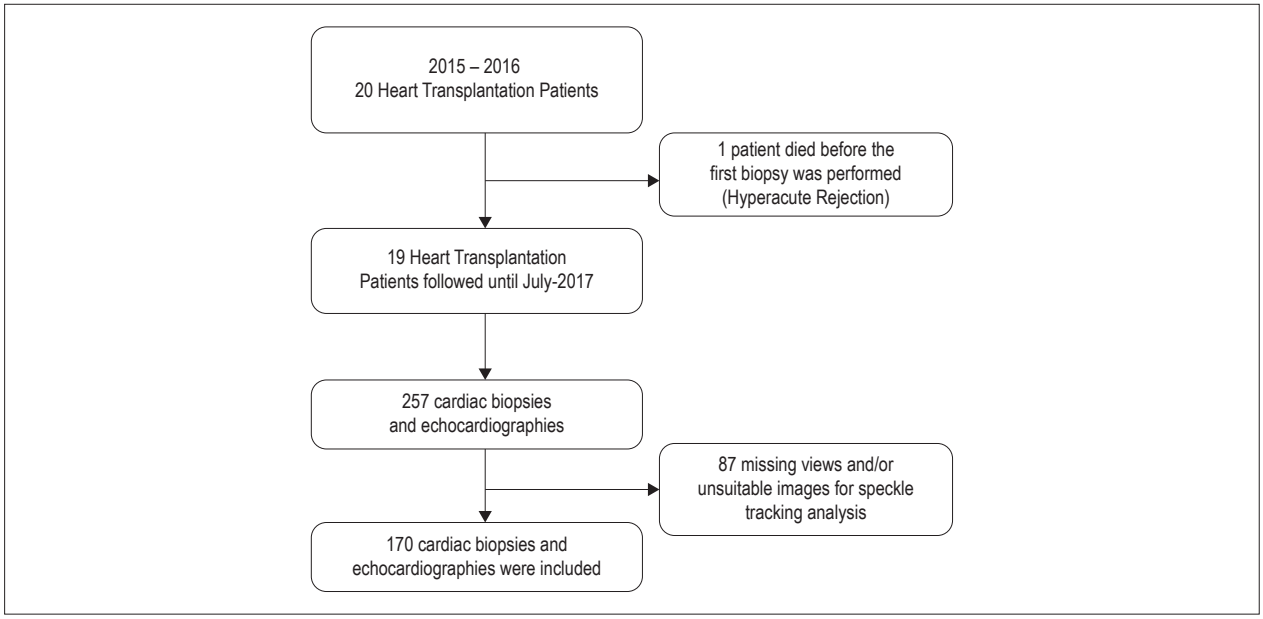

Figure 1 – *Feasibility of strain evaluation by speckle-tracking analysis.*

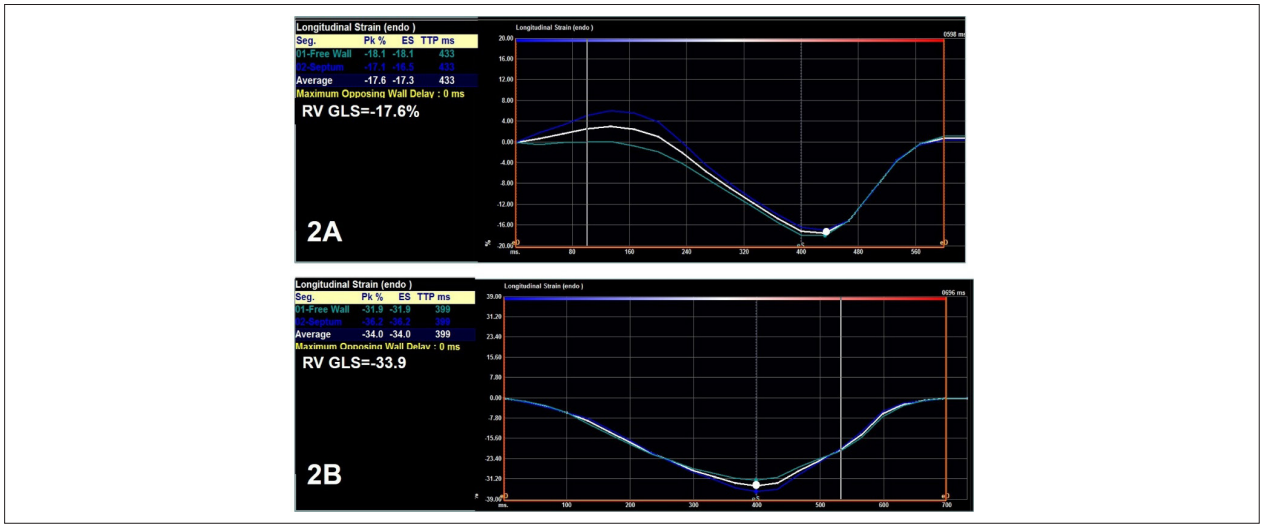

Figure 2 – *Two-dimensional speckle tracking imaging for right ventricular analysis in a heart transplant recipient at the time of biopsy-proven 2R rejection (Panel 2A) and the same patient at the time of biopsy without rejection (Panel 2B). Curves represent longitudinal strain curves and the white dot represents peak-systolic strain, which were used to measure right ventricular systolic function.*

analyzed in this study, 15 biopsies from 12 HTx recipients showed 2R rejection, and 155 biopsies showed either no evidence of cellular rejection or 1R rejection (n = 130 and n = 25, respectively).

Heart Structure and Function

Compared to exams from patients without rejection or 1R rejection, echocardiograms from corresponding biopsies with 2R rejection episodes revealed greater LV posterior wall thickness, which did not reflect in an increase in LV mass or relative wall thickness. In exams from patients with 2R rejection, measures of diastolic function showed an increase in the medial and lateral E/e' ratio and the E/A ratio (Table 2).

LV systolic function did not differ between groups when evaluated by the traditional method (LVEF) or by LV GLS (−20.2 ± 3.3% in the 0R/1R group vs. −19.5 ± 3.3% in the 2R group, p = 0.351). On the other hand, RV systolic function was reduced in the 2R group, in comparison with the other group, when evaluated by TAPSE, S wave and RV FAC. Additionally, RV GLS (−22.97 ± 4.4% in the 0R/1R group vs. −20.6 ± 4.9% in the 2R group, p = 0.038) was reduced in the 2R group, in comparison with the 0R/1R group (Figure 3).

Table 1 – Baseline characteristics of the study population

Variable	Value
HTx recipientes (n = 19)	
Male sex, n (%)	8 (42%)
Age at transplantation (years)	47.7 ± 12.4
Comorbidities	
Diabetes, n (%)	5 (25%)
Hypertension, n (%)	4 (20%)
Obesity, n (%)	4 (20%)
Stroke, n (%)	5 (25%)
Dyslipidemia, n (%)	1 (5%)
Peripheral vascular disease, n (%)	3 (15%)
Current smoker, n (%)	7 (35%)
Time to HTx (days)	80 ± 105
Ischemic time before HTx (min)	225 ± 57
Heart failure etiology	
Ischemic heart disease, n (%)	2 (10%)
Non-ischemic cardiomyopathy, n (%)	17 (89%)
Donor	
Men, n (%)	13 (65%)
Age (years)	29 ± 7.6
Body surface area (m^2)	1.78 ± 1.4
Current smoker, n (%)	0 (0%)

Data shown as mean ± SD or n (%). Number of patients = 19. HTx: heart transplantation.

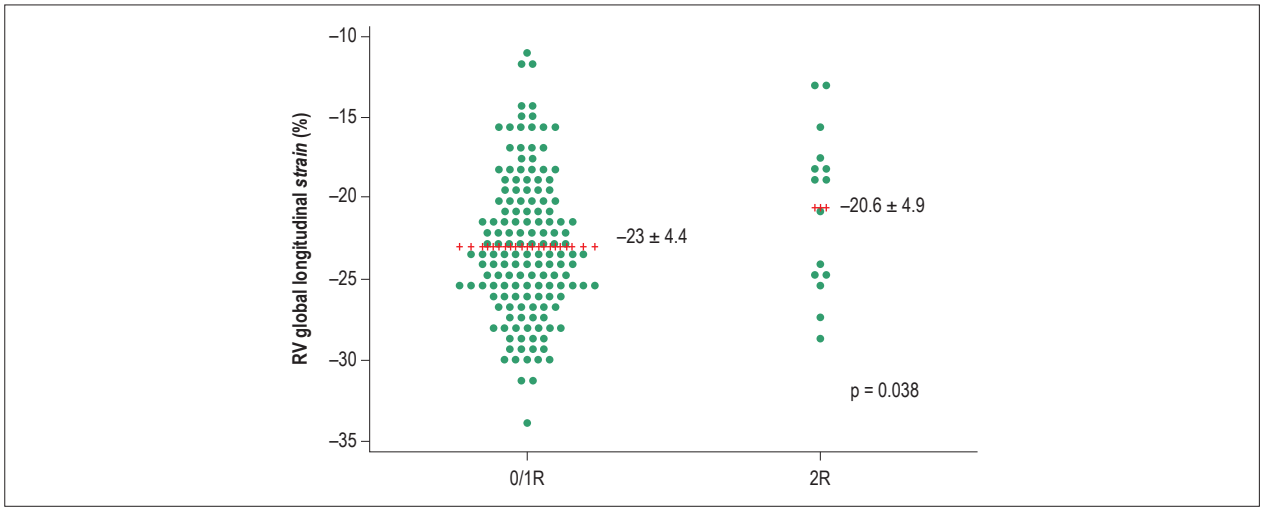

Figure 3 – *Distribution of rejection on cardiac biopsies over RV GLS strain results after heart transplantation.*

Discussion

In this retrospective analysis of 170 matched echocardiograms and endomyocardial biopsies of post-HTx patients, our main finding was that moderate (2R) cellular rejection was associated with RV contractile dysfunction when assessed by RV GLS, as well as by conventional echocardiographic parameters such as TAPSE, S wave, and FAC. Conversely, LV systolic function was unchanged in this group. In addition, moderate rejection was associated with increased LV posterior wall thickness, E/e' ratio, and E/A ratio.

In the search for noninvasive methods to aid in screening for cellular rejection, a few studies evaluated strain and strain rate

Table 2 – Cardiovascular structure and function

Variables	0R/1R N = 155	2R N = 15	p-value
Aortic diameter (mm)	33.0 ± 4.1	32.4 ± 5.7	0.575
Left atrial diameter (mm)	40.8 ± 5.6	42.5 ± 7.7	0.372
IS thickness (mm)	11.2 ± 1.4	11.5 ± 1.6	0.439
PW thickness (mm)	10.4 ± 1.4	11.3 ± 1.5	0.013
Relative wall thickness	0.49 ± 0.08	0.53 ± 0.08	0.115
LV end-diastolic diameter (mm)	42.4 ± 4.1	43.0 ± 2.7	0.550
LV end-systolic diameter (mm)	28.2 ± 4.4	28.3 ± 3.7	0.936
LV end-diastolic volume (mL)	88.2 ± 24.3	84.6 ± 18.0	0.593
LV end-systolic volume (mL)	35.7 ± 12.9	37.2 ± 12.9	0.618
RV basal diameter (mm)	40.2 ± 4.4	40.9 ± 2.9	0.550
RV end-diastolic area (cm^2)	20.2 ± 4.3	21.4 ± 3.8	0.302
RV end-systolic area (cm^2)	10.9 ± 3.1	12.8 ± 3.8	0.024
LV mass (g)	157.2 ± 33.9	173.9 ± 33.7	0.057
LV ejection fraction, Teichholz (%)	62.3 ± 7.9	63.2 ± 8.4	0.714
LV ejection fraction, Simpson (%)	59.6 ± 7.9	56.5 ± 8.6	0.122
TAPSE (mm)	13.8 ± 3.4	10.9 ± 2.2	0.009
RV fractional area change (cm/s)	46.2 ± 8.6	40.8 ± 10.2	0.016
E/A	1.56 ± 0.55	2.07 ± 0.82	0.017
Deceleration time (ms)	183.0 ± 41.8	158.2 ± 20.8	0.157
Medial e' (cm/s)	7 ± 2	7 ± 2	0.653
Lateral e' (cm/s)	12 ± 3	9 ± 2	0.100
Medial E/e'	11.9 ± 4.4	20.6 ± 4.4	0.001
Lateral E/e'	7.6 ± 3.5	13.3 ± 5.2	0.006
S wave (cm/s)	10.0 ± 2.1	8.3 ± 1.8	0.035
LV global longitudinal strain (%)	−20.2 ± 3.3	−19.5 ± 3.3	0.351

Data are shown as mean ± SD. P-value calculated by ANOVA adjusted for heart transplantation patients. E/A: early to late mitral inflow velocity ratio; e': mitral relaxation velocity; E/e': mitral inflow to mitral relaxation velocity ratio; IS: interventricular septal; LV: left ventricular; PW: posterior wall; RV: right ventricular; S wave: tricuspid lateral systolic velocity; TAPSE: tricuspid annular plane systolic excursion.

by tissue Doppler imaging (TDI). Marciniak et al.,[10] studying a group of 31 patients with 106 biopsy/echocardiogram pairs, demonstrated a decrease in strain and strain rate on TDI in basal and apical segments of the RV free wall and in basal and middle segments of the LV lateral wall in the group with ≥ 1B rejection, suggesting that these findings could be an additional tool for detecting acute rejection. The same authors also observed that, when histopathological involvement was mild (< 2B), these alterations took on a pattern of segmental involvement, with little or no impact on GLS, revealing a low sensitivity of the latter for low-grade rejection.[10] More recently, the advent of evaluation of regional or global myocardial function by speckle tracking has provided a more robust technique for the detection of subclinical myocardial dysfunction, overcoming the limitations of TDI-measured strain, especially the dependence on prospective acquisition and the angle of acquisition.[10,11] At least three studies, published almost concomitantly, showed a rejection-related decrease in LV GLS,[14-16] while another group, as in our study, found no such differences in LV GLS when comparing exams from patients with no rejection or mild rejection to patients with moderate rejection.[17] It bears stressing that, even in the 0R group of our study, LV GLS values exceeded the range reported as normal after HTx in the literature.[18,19]

Evaluation of RV parameters as potential markers of subclinical rejection was relatively less explored in previous studies. Clemmensen et al. studied a group of 36 HTx recipients and found that TAPSE was reduced in the group with cellular rejection.[16] Another group, which studied a similar number of patients (n = 34), found a reduction in RV free wall strain associated with ≥ 2R rejection.[15] These findings were observed as a similar trend in our study, where the decrease in RV function was shown by TAPSE, S wave, FAC, and RV peak GLS in moderate rejection. Eleid et al. demonstrated a decline in LV GLS in the early post-HTx period, and the association of non-improvement in GLS throughout follow-up was an independent predictor of worse prognosis for these patients, regardless of the histopathological results of endomyocardial biopsies.[20]

In addition, the early post-Htx period is a time of adaptation of the new heart to the thoracic space, in a different position in the chest compared to the native heart, with expected structural alterations like increase of LV mass and in wall thickness due to inflammatory cell infiltration and graft edema, which are part of the physiological process of Htx. These abnormalities improve gradually within the first 6 months after transplant, but they can be a confounders of some signs of graft rejection.

Furthermore, in agreement with the findings of our study, LV hypertrophy and changes in diastolic function, especially in LV filling pressure, have been associated with cellular rejection, despite the lower sensitivity of these findings, which may be confused with usual post-HTx alterations.[15,18]

Some limitations of this analysis should be noted. As most echocardiographies for which corresponding biopsies were available had been performed to detect complications of endomyocardial biopsy, such as pericardial effusion and tricuspid valve injury, many failed to include a detailed evaluation of cardiac function and dynamics. As a consequence, we had to exclude 34% of biopsies. The single-center design of this study is also a limitation, especially because it was performed at a facility that is still expanding its HTx program, which accounts for the small sample size. Information on antibody-mediated rejection was not included in this study; therefore, echocardiographic findings cannot be extrapolated for that situation. Overall, the study comprised a low immunological risk population.

Conclusions

In conclusion, we found evidence of RV systolic dysfunction in post-HTx patients with moderate rejection by 2D STE assessment of strain, as well as by conventional echocardiographic methods, in comparison with patients with no significant signs of rejection on histopathology. LV systolic function remained unchanged, suggesting that subclinical LV dysfunction may arise later than RV dysfunction. Moreover, patients with biopsy evidence of moderate rejection had greater LV hypertrophy and worse LV diastolic function and filling pressure on echocardiography. The role of these findings in screening for and diagnosing rejection, perhaps even leading to practice-changing updates in endomyocardial biopsy protocols, has yet to be explored in a prospective multicenter study.

Author contributions

Conception and design of the research and Analysis and interpretation of the data: Carrion LFBM, Rohde LE, Santos ABS; Acquisition of data, Statistical analysis and Writing of the manuscript: Carrion LFBM, Santos ABS; Critical revision of the manuscript for intellectual content: Sperotto A, Nazario R, Goldraich LA, Clausell N.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the UFRGS – Hospital de Clínicas de Porto Alegre under the protocol number CAAE 68562717.9.0000.5327. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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