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Research Letter

Natural recovery of cardiac allograft diastolic function, a retrospective longitudinal report

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ABSTRACT

Cardiac allografts suffer diastolic dysfunction early post-heart transplantation (HTx) due to ischemic injury, however the natural course of diastology recovery post HTx remains unknown (Tallaj et al., 2007 [1]). We retrospectively reviewed 60 adult HTx patients between 2015 and 2021 at a single site. Invasive hemodynamics and echocardiograms were obtained at 2 weeks and 1, 3, 6, and 12 months post-HTx. RA strain by 2D feature tracking was compared to intracardiac pressure measurements. In all patients, we observed normalization of RV and RA filling pressures by post-operative week 12 and recovery of diastolic dysfunction by month 6. There was an inverse correlation between RV end-diastolic pressure and RA contractile ($r = -0.192$, $p < 0.05$) and reservoir ($r = -0.128$, $p < 0.05$) functions in the allograft. As the post-transplant care paradigm shifts away from invasive procedures, right atrial indices should be included in imaging-based allograft surveillance studies.

1. Introduction

Heart transplantation (HTx) involves transplanting a heart that has sustained an acute ischemic injury into a recipient body that has been critically ill and just underwent major cardiac surgery. As such, donor hearts frequently develop diastolic dysfunction post-HTx, more commonly within the first two months of transplant (~20 %), which is a risk factor for mortality [1]. While primary systolic graft failure, rejection, and cardiac allograft vasculopathy are associated with impaired diastolic function, those with uncomplicated post-HTx course almost invariably experience exercise limitation and diuresis dependence early post-HTx; indicating impaired diastology of the allograft [2–4]. Classic echocardiographic indices of myocardial relaxation have limited usability due to graft adhesion to mediastinal structures [5]. Left atrial (LA) strain can quantitate diastolic function as it captures the interplay between atrial and ventricular pressure [6]. In the HTx population, right atrial (RA) strain is more attractive than LA strain due to the preserved atrial wall structure for bicaval donor heart anastomosis.

This study aims to describe the expected recovery course of cardiac allografts diastolic function in the early post-HTx period. We examined the utility of noninvasive RA strain by transthoracic echocardiography (TTE) in monitoring this recovery, as validated against invasive hemodynamics of right heart catheterization.

2. Methods

We retrospectively evaluated adult patients who underwent HTx performed at the University of Florida Shands hospital between 01/2015 and 02/2021. Inclusion criteria include first HTx, bicaval anastomosis, donation after brain death, and follow-up for at least one year post-HTx. Exclusion criteria include primary graft dysfunction, pericardial effusion requiring intervention, mortality or cardiac hospitalization within the first year, or any rejection within the first year. Rejection was defined as International Society for Heart and Lung Transplantation ≥2R, or clinical, immunologic, or histological antibody-mediated rejection.

Echocardiograms were performed using commercially available ultrasound systems (Phillips EPIQ CVx machine using X5–1 transthoracic scanning probe) according to national guidelines. Strain analysis was performed via Tomtec software (version 1.2) on non-contrasted 2D TTE images in a semiautomated fashion. Continuous variables are expressed as means ± SD. Pearson's correlation coefficients were calculated to compare noninvasive and invasive measurements. Means were compared using independent sample *t*-test. Cardiac cycle times were corrected to heart failure using the Bazett method. Analysis was performed using IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

Raw TTE images and right cardiac catheterization (RHC) waveform data were reviewed retrospectively. Per routine practice, invasive hemodynamic data included RA mean pressure and right ventricular end-diastolic pressure (RVEDP), measured at end-expiration after recalibrating the transducer at the mid-axillary level. Along with basic 2D analysis of RA and right ventricular (RV) function, we studied the RA strain as previously described by Nagueh et al. [5] The above datapoints were captured at 2 weeks, 1 month, 3 month, 6 months, and 12 months post-HTx. This study was approved by the institutional review board of the University of Florida. Patient data was entered using a standardized data collection platform.

3. Results

A total of 60 individuals met study criteria and had complete hemodynamic and TTE data. Patient demographics are described in Table 1 whereas longitudinal hemodynamics and TTE measurements are represented in Table 2 and Table 3, respectively. The mean ischemic time for our cohort was 197.8 (±41.0) minutes. None of the patients had significant donor-specific antibodies. Both TTE and RHC show progressive improvement in right-sided diastolic function during the first three months. We found a correlation between the two methods in this

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Table 1
Patient characteristics.

Variable - pretransplant	Prevalence
Sex, n (%)	
Male	44 (73.3)
Female	16 (26.7)
Age, mean (±SD)	45.7 (±14.2)
Race, n (%)	
Caucasian/White	42 (70.0)
Black/African American	12 (20.0)
Asian/Pacific Islander	2 (3.3)
Other	4 (6.7)
Ethnicity, n (%)	
Hispanic/Latino	6 (10.0)
Not Hispanic/Latino	54 (90.0)
BMI, mean (±SD)	27.7 (±5.76)
Cardiovascular risk factors, n (%)	
Diabetes	12 (20.0)
Hypertension	38 (63.3)
Hyperlipidemia	56 (93.3)
Obesity	18 (30.0)
Tobacco use	23 (38.3)
Primary Cardiomyopathy, n (%)	
Non-ischemic cardiomyopathy/chronic systolic heart failure	33 (55.0)
Ischemic cardiomyopathy	13 (21.7)
Congenital conditions	10 (16.7)
Other	4 (6.7)

HTx cohort with an uncomplicated postoperative clinical course. While RVEDP reflects RV stiffness, RA reservoir and contractile strain reflect RA compliance and active ejection function, both of which are affected by RA afterload.

We observed a steady decline in the RA mean pressure and RVEDP measurements over the first 6 months post-transplant (Fig. 1). This was accompanied by parallel increases in RA ejection fraction, reservoir, conduit, contractile, global strain, and fractional area change over time. Comparing right-sided invasive and non-invasive indices, we found that RA pressure, RA fractional area change, and RA area were the only values that significantly improved (Table 2). There were significant correlations between mean RA pressure and RV area (both end-systolic and end diastolic), RA contractility, RA reservoir strain, RA fractional area change, and RA global longitudinal strain. The RA reservoir strain correlated with RVEDP ($r = -0.145$, $p = 0.036$), which is intuitive as both occur during the same cardiac cycle.

Evidence for using atrial strain to diagnose and quantify diastolic dysfunction is quickly mounting. Several studies have shown that LA global PALS (peak atrial longitudinal strain) accurately identifies LV diastolic dysfunction and strongly correlates with LV filling pressures obtained by catheterization [7–9]. To our knowledge, this is the first study that demonstrates the correlation between RA contractility and reservoir strain with the RV filling pressures in the donor heart. Persistent exertional dyspnea post-HTx transplantation despite normal ventricular function may be associated with atrial failure, a recently recognized entity that has not been well studies in cardiac allografts [10].

Readers should be cognizant of the following limitations of our report. First, this is a retrospective analysis and may be subject to altered management and data acquisition practices over the years. Additionally, this is a single center study, which may limit generalizability. While we describe normal, we do not compare normal to abnormal cases. Incorporating imaging indices of RA and RV function in clinical allograft surveillance practice requires prospective validation, likely in combination with serum biochemical markers of graft injury.

Table 2
Baseline and follow up invasive and noninvasive right heart diastolic function measurements.

	Baseline		6 months		Interval change	
	Mean	SD	Mean	SD	Mean	*P* value
Hemodynamic variable						
RA pressure	10.85	5.84	6	3.04	−4.85	**0.007**
RVEDP	12.27	5.96	8.43	5.52	−3.84	0.231
PASP	35.41	8.86	27.21	6.31	−8.2	0.054
PADP	17.09	5.77	17.32	28.67	0.23	0.207
Mean PAP	23.41	6.44	18.07	4.89	−5.34	0.129
HR	91.98	10.5	92.07	10.13	0.09	0.629
Systolic BP	131.11	14.28	136.63	17.69	5.52	0.215
Diastolic BP	79.85	9.63	90.24	11.62	10.39	0.21
CO Fick	5.47	1.25	5.65	1.65	0.18	0.899
RV echo measurements						
RV end diastolic diameter	4.56	0.76	4.37	0.91	−0.19	0.174
RV free wall strain	8.69	4.85	9.04	4.74	0.35	0.738
RV fractional area change (%)	19.11	8.43	17.6	7.46	−1.51	0.217
RV end systolic surface area (cm2)	20.87	5.18	22.92	6.53	2.05	0.351
RV end diastolic surface area (cm^2)	25.62	5.68	27.72	7.54	2.1	0.15
RV global longitudinal strain (negative)	−8.59	−4.32	−9.39	−4.06	−0.8	0.397
RAS- Contractile (negative)	−8.45	−4.41	−9.94	−7.63	−1.49	0.108
RAS – Conduit (negative)	−13.15	−7.28	−16.8	−7.73	−3.65	0.662
Reservoir	10.79	7.45	14.73	7.15	3.94	0.873
RA fractional area change (%)	15.32	6.52	19	11.14	**3.68**	**0.03**
RA end systolic surface area (cm^2)	68.91	34.61	60.64	26.19	**−8.27**	**0.007**
RA end diastolic surface area (cm^2)	57.11	29.11	48.09	25.03	−9.02	0.099
RA ejection fraction (%)	18.8	10.57	22.35	11.96	3.55	0.573
RA peak longitudinal strain (positive)	12.02	6.65	13.84	7.54	1.82	0.39

4. Discussion

This study examined the natural pattern of diastolic recovery of cardiac allograft post-HTx. We found that cardiac allograft diastolic function recovers during the first 6 months post-HTx and can be monitored using RA and RV echocardiographic indices. These measurements could be incorporated in future surveillance protocols of allograft dysfunction. As the transplant community mounts interest in noninvasive allograft monitoring protocols which usually include either TTE or cardiac magnetic resonance, our data can serve as a reference for "normal" and the basis of designing studies incorporating RA echocardiographic indices to define the threshold for different complications.

Table 3
Pearson's correlation coefficients between echocardiography and invasively measured right heart diastolic function.

Variable	Echo vs. mean RA pressure		Echo vs. RVEDPs	
	Pearson correlation coefficient, r	P value	Pearson correlation coefficient, r	P value
RV EDD	−0.117	0.090	−0.058	0.403
RV free wall strain	−0.010	0.879	0.044	0.526
RV fractional area change (%)	0.093	0.177	−0.008	0.908
RV end systolic surface area (cm^2)	**−0.165**	**0.016**	−0.068	0.329
RV end diastolic surface area (cm^2)	**−0.151**	**0.026**	−0.072	0.296
RV global longitudinal strain (negative)	−0.51	0.461	0.011	0.871
RAS- Contractile (negative)	**−0.272**	**0.010**	−0.171	0.106
RAS – Conduit (negative)	−0.79	0.252	−0.088	0.203
Reservoir	**−0.202**	**0.003**	−0.145	0.036
RA fractional area change (%)	**−0.141**	**0.041**	−0.072	0.297
RA end systolic surface area (cm^2)	**0.185**	**0.007**	0.003	0.962
RA end diastolic surface area (cm^2)	**0.190**	**0.005**	0.016	0.812
RA ejection fraction (%)	−0.062	0.372	−0.061	0.378
RA free wall strain	**−0.154**	**0.025**	−0.058	0.400

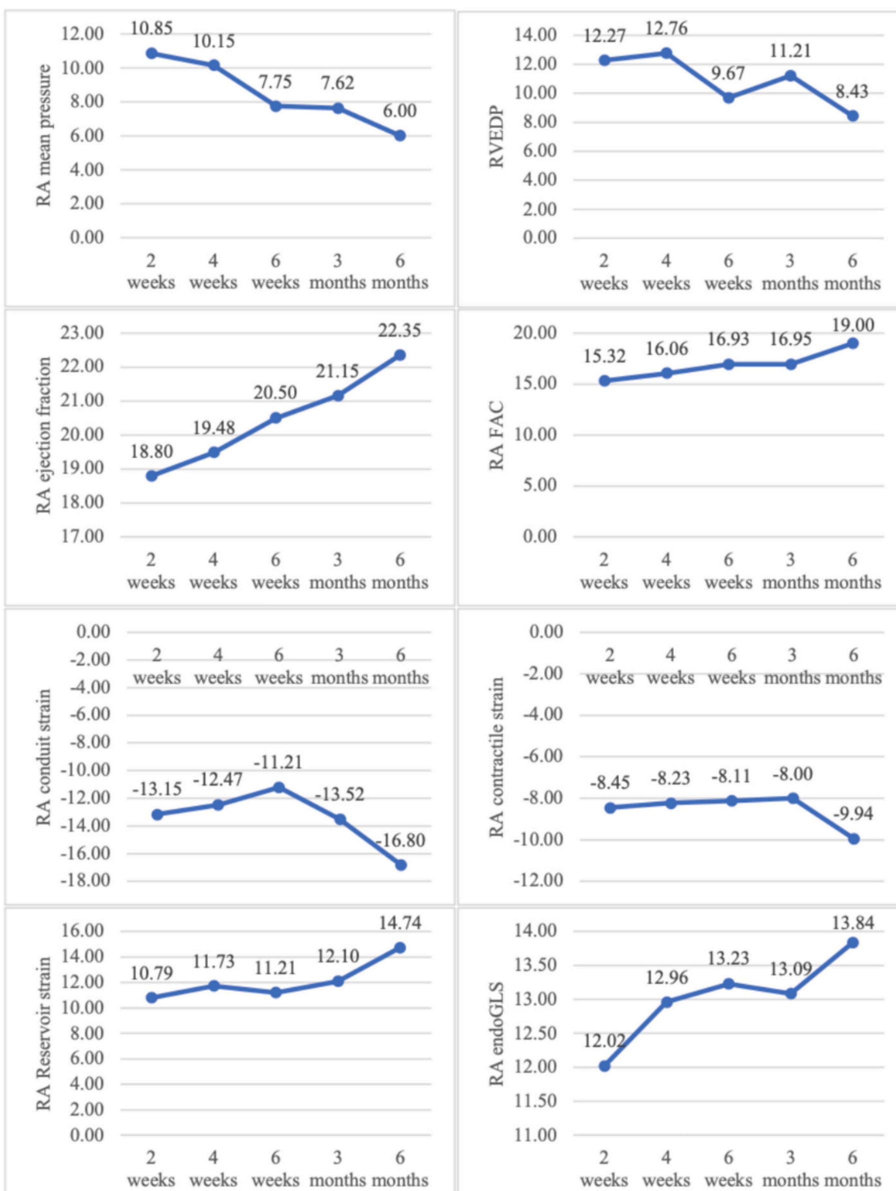

Fig. 1. Trends of invasive and noninvasive allograft diastolic indices in a cohort with uncomplicated post-transplantation clinical course. A steady decline in the right atrial mean pressure and right ventricular end diastolic pressure measurements can be observed over the initial six months of uncomplicated cardiac transplantations.

Ethical statement

This study was approved by the University of Florida Institutional Review Board (IRB202003168) and performed in compliance with relevant laws and institutional guidelines. Informed consent was waived given minimal risk to participants.

CRediT authorship contribution statement

Shengyi Fu: Writing – review & editing, Writing – original draft, Project administration, Formal analysis, Data curation. **Aditi G.M. Patel:** Formal analysis, Data curation. **Mohammed Ruzieh:** Investigation, Formal analysis. **Seri Hanayneh:** Writing – original draft, Data curation. **Juan Vilaro:** Visualization, Supervision, Methodology, Conceptualization. **Mustafa M. Ahmed:** Conceptualization. **Juan M. Aranda:** Visualization, Supervision, Conceptualization. **Alex M. Parker:** Writing – original draft, Conceptualization. **Mark S. Bleiweis:** Supervision, Conceptualization. **Jeffrey P. Jacobs:** Validation, Supervision, Conceptualization. **Mohammad A. Al-Ani:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

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