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ORIGINAL ARTICLE

Clinical features, exercise hemodynamics, and determinants of left ventricular elevated filling pressure in heart-transplanted patients

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cardiac allograft vasculopathy, global longitudinal systolic function, heart transplantation, hemodynamics, positron emission tomography.

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Summary

This study aimed to assess clinical, functional, and hemodynamic characteristics of heart-transplanted (HTX) patients during exercise. We performed comprehensive echocardiographic graft function assessment during invasive hemodynamic semi-supine exercise test in 57 HTX patients. According to hemodynamics findings, patients were divided into Group A: normal left ventricular (LV) filling pressure (FP): pulmonary capillary wedge pressure (PCWP) <15 mmHg at rest and <25 mmHg at peak exercise, and Group B: elevated LV-FP: PCWP ≥15 mmHg at rest or ≥25 mmHg at peak exercise. Thirty-one patients (54%) had normal LV-FP and 26 patients (46%) had elevated LV-FP. The latter had higher cumulative rejection burden ($P < 0.01$) and were more symptomatic (NYHA class >1) ($P < 0.05$), and cardiac allograft vasculopathy (CAV) was more prevalent ($P < 0.05$). With exercise, the changes in both left- and right-sided filling pressures were significantly increased, whereas LV longitudinal myocardial deformation was lower ($P < 0.05$) in patients with elevated LV-FP than in patients with normal LV-FP. No between-group difference was observed for cardiac index or LV ejection fraction (LVEF) during exercise. In conclusion, elevated LV-FP can be demonstrated in approximately 50% of HTX patients. Patients with elevated LV-FP have impaired myocardial deformation capacity, higher prevalence of CAV, and higher rejection burden, and were more symptomatic. Exercise test with the assessment of longitudinal myocardial deformation should be considered in routine surveillance of HTX patients as a marker of restrictive filling (ClinicalTrials.gov Identifier: NCT02077764).

Introduction

Elevated left ventricular (LV) filling pressure (FP) is common in cardiovascular diseases such as cardiomyopathies, myocardial deposit disease (i.e., amyloidosis), end-stage ischemic heart disease, and valvular heart disease. The presence of restrictive filling in these diseases is associated with reduced functional capacity, impaired quality of life, and poor prognosis [1,2]. Elevated LV-FP is also clinically recognized among heart-transplanted (HTX) patients [3]. However, the prevalence, clinical characteristics, graft function implications, and mechanisms leading to elevated LV-FP are poorly understood [4]. Development of myocardial fibrosis in HTX patients has been described in serial investigations of endomyocardial biopsies [5,6], and the degree of myocardial fibrosis correlates with elevated LV-FP in patients undergoing re-HTX [4]. The presence of elevated LV-FP is often assessed noninvasively by echocardiographic Doppler measurement, which poorly correlates with invasive pressure measurements in HTX patients [7–9]. Only

one recent study has evaluated the LV filling response to exercise in HTX patients. In that study, 18% of patients had elevated pulmonary capillary wedge pressure (PCWP) at rest, whereas 67% showed elevated PCWP during exercise [7], which indicates impaired LV diastolic reserve in these HTX patients.

Exercise capacity is generally limited to approximately 50–70% of the age-predicted value in HTX patients despite normal LV ejection fraction (LVEF) and independent of the presence of cardiac allograft vasculopathy (CAV) [10–15]. It has been speculated that the reduction in exercise capacity observed in HTX patients may be caused by elevated LV-FP [7,16,17].

The aim of this study was to assess the clinical characteristics and graft function by myocardial deformation analysis and invasive hemodynamic assessment at rest and during exercise in a cohort of HTX patients.

Methods

Patients

The study population consisted of 57 HTX patients who were included at the time of routine angiography during the period from September 2013 until February 2015. Patients ≥18 years of age were included after informed and written consent according to the principles of the Helsinki Declaration. The study was approved by the local scientific ethical committee of the Central Denmark Region. The patients underwent a symptom-limited, semi-supine exercise test with simultaneous right heart catheterization (RHC) in addition to coronary angiography and 15O-H_2O positron emission tomography (PET). We divided the patients into two groups according to the hemodynamic findings: Group A: Normal LV-FP: PCWP < 15 mmHg at rest and <25 mmHg at peak exercise; Group B: Elevated LV-FP: PCWP ≥15 mmHg at rest or ≥25 mmHg at peak exercise.

We performed a subgroup analysis in which we compared patients with elevated LV-FP with and without significant CAV (International Society of Heart and Lung Transplantation (ISHLT) CAV classes 2 and 3).

Invasive hemodynamic measurements

RHC was performed using a standard 7.5-F triple-lumen Swan-Ganz catheter (Edwards Lifesciences, Irvine, CA, USA). The catheter was introduced ultrasound guided using the Seldinger technique [18] into the right internal jugular vein and advanced guided by pressure and fluoroscopy to the pulmonary artery (PA). PCWP, mean right atrial pressure (mRAP), systolic and diastolic PA pressure (sPAP, dPAP), mean PA pressure (mPAP), transpulmonary gradient (transpulmonary gradient = mPAP-PCWP), cardiac output (CO), arteriovenous oxygen difference, and blood pressure (BP) were measured at rest, at each level of exercise until exhaustion, and after 5 min of postexercise rest. PCWP at rest and postexercise were measured at end-expiration. During exercise, a mean PCWP was used. Based on previous studies of healthy individuals, we considered a PCWP at rest exceeding 15 mmHg and/or 25 mmHg during exercise to be abnormally increased [19–24].

Cardiac output was measured using thermodilution as an average of two measurements not differing more than 10%, and indexed to body surface area as cardiac index (CI). Stroke volume (SV) was calculated as CO divided by heart rate (HR). Pulmonary artery compliance (PAC) was calculated as follows: SV/(sPAP-dPAP). Pulmonary vascular resistance index (PVRI) was calculated as follows: PVRI = 80 × (mPAP-mPCWP)/CI. Systemic vascular resistance index (SVRI) was calculated as follows: SVRI = 80 × (mean arterial pressure (MAP)-mRAP)/CI. Oxygen consumption (VO2) was calculated using the indirect Fick by the following: VO2 = CO × arteriovenous oxygen difference × 1.36 × hemoglobin (g/dl) × 10. Arteriovenous oxygen content difference was measured as the difference between pulsoxymetry and directly measured PA-O2 content at rest and peak exercise.

Exercise protocol

All patients performed a multistage symptom-limited, semi-supine bicycle exercise test using the Echo Cardiac Stress Table (Lode B.V., Netherlands). Workload started at 0 W and was increased by 25 W every 3 min. Patients were encouraged to maintain a fixed pedaling speed of 60 rounds per minute and to exercise until exhaustion (Borg > 18)[25].

Echocardiography

We used a commercially available ultrasound system (Vivid 9, GE Healthcare Horten, Norway) with a 3.5-MHz-phased array transducer (M5S).

At rest, patients underwent a comprehensive echocardiographic assessment according to current guidelines [26]. Using two-dimensional speckle tracking analysis, we assessed LV global longitudinal strain (LV-GLS) and averaged the values from three apical views.

At each stage of exercise, cine loops and tissue Doppler images from all three apical views along with pulsed wave Doppler of the mitral inflow and left ventricular outflow tract were assessed, and LVEF was calculated by the biplane method of disks. Peak systolic mitral annular velocities (S') were estimated from the tissue Doppler velocity images as an average of septal, lateral, anterior, and posterior

velocities. The magnitude of LV-GLS [27] was obtained from frame-by-frame tracking of speckle patterns in standard two-dimensional cine loops. The speckle area of interest was manually adjusted for optimal tracking results. Segments with unacceptably low tracking quality were excluded. LV-GLS was calculated at the time in systole when the value peaked using a 17-myocardial segment model [28]. We have previously reported low inter- and intraobserver variability in an HTX population for LV-GLS [29].

Data were analyzed offline using dedicated software (EchoPAC PC SW-Only, 113, GE Healthcare, Milwaukee, WI, USA) by a single investigator (TSC) blinded to clinical status and invasive measurements.

Coronary angiography

Coronary angiography was performed through a 6-F sheath inserted in the right femoral artery. Coronary arteries were imaged after administering intracoronary nitroglycerin (200 μg). At least two projections of each coronary artery were acquired. All angiographies were reviewed by an experienced cardiologist, blinded to hemodynamic and the patient's clinical status. CAV was classified according to the ISHLT guidelines [30].

Positron emission tomography

Positron emission tomography scans were performed to evaluate the function of the micro- and macrovascular system by obtaining quantitative measure of myocardial blood flow. The PET scans were performed before and after adenosine challenge on a Siemens Biograph 64 TruePoint TrueV PET/CT (Siemens Healthcare, Erlangen, Germany). All subjects abstained from caffeine for 24 h before testing. A low-dose computed tomography scan was performed for attenuation correction. Afterward, a 6-min list-mode emission scan was started simultaneously with bolus injection of 400 MBq of 15O-H_2O. Adenosine infusion (140 μg/kg/min) was started 2 min before the second injection of 15O-H_2O and continued during the PET scan. Emission data were reconstructed into a dynamic scan consisting of 22 time frames (1×10 s, 8×5 s, 4×10 s, 2×15 s, 3×20 s, 2×30 s, and 2×60 s) with a matrix size of 4 mm × 4 mm × 4 mm per frame using the TrueX reconstruction algorithm (three iterations, 21 subsets, postfilter 5 mm 3D Gaussian). Dynamic data were analyzed using Cardiac VUer [31]. We calculated coronary flow reserve (CFR) as the ratio between hyperemic and resting blood flow. One patient developed AV block during adenosine administration and four patients declined to participate in the PET scans.

Endomyocardial biopsy

Previous acute cellular rejection episodes were histopathologically graded in three forms, according to the ISHLT guidelines [32], and biopsy scores were calculated as previously described [33].

Statistical methods

Normally distributed data are presented as mean ± standard deviation; non-normally distributed are presented as median and interquartile range. Categorical data are presented as absolute values with percentages. Histograms and Q-Q plots were used to check continuous values for normality. Between-group differences were assessed by *t*-test for normally distributed data and Mann–Whitney *U*-test for non-normally distributed data. A linear regression model was used to compare continuous variables, and predicted value and residual were used to check the regression models. Logistic regression was used in the univariate analysis. All tests were two-sided, and $P < 0.05$ was considered statistically significant. Analyses were performed using STATA (STATA/IC 12, StataCorp LP, College Station, TX, USA).

Results

Patient characteristics

Thirty-one patients (54%) were classified with normal LV-FP and 26 patients (46%) with elevated LV-FP. The clinical characteristics of the two groups are shown in Table 1. Patients in the elevated LV-FP group were more likely to have NYHA class >1 ($P = 0.03$), higher cumulative number of previous rejection ≥2R ($P = 0.001$), and CAV ($P = 0.046$) than patients in the normal LV-FP group.

Blood samples revealed higher creatinine ($P = 0.02$), troponin-T ($P < 0.01$), and NT-proBNP (0.03), whereas hemoglobin was significantly lower ($P = 0.02$) in patients in the elevated LV-FP than in patients with normal LV-FP.

Micro- and macrovascular dysfunction

Micro- and macrovascular parameters are shown in Table 1. Eleven patients (42%) with elevated LV-FP had significant CAV (ISHLT classes 2 or 3) versus seven (23%; $P = 0.11$) patients with normal LV-FP. PET examinations revealed no significant differences between the two groups in myocardial blood flow at rest ($P = 0.83$). Inversely, trends were observed toward lower myocardial blood flow during hyperemia ($P = 0.08$), and reduced CFR ($P = 0.06$) was observed in the elevated LV-FP group. In a subgroup analysis looking at microvascular function, patients with

Table 1. Patient characteristics, micro-, and macrovascular dysfunction.

	Normal LV filling pressure (n = 31)	Elevated LV filling pressure (n = 26)	P
Male (%)	65%	81%	0.18
Donor age (years)	42 ± 11	43 ± 13	0.78
Age (years)	52 ± 14	55 ± 10	0.39
Time since transplantation (years)	7.5 ± 6.1	10.9 ± 6.0	0.04*
NYHA functional class >1 (%)	16	42	0.03*
Diabetes (%)	16	23	0.52
Hypertension (%)	87	85	0.79
Number of EMBs showing ≥2R	0.4 ± 0.6	1.3 ± 1.3	0.001*
Rejection score	7.8 ± 4.1	11.2 ± 6.6	0.02*
Medication			
Prednisolone (%)	42	27	0.24
Cyclosporine (%)	32	50	0.18
Tacrolimus (%)	68	50	0.18
Mycophenolate (%)	77	69	0.49
Everolimus (%)	19	42	0.06
Statins (%)	90	85	0.52
ACE/ATII inhibitor (%)	74	69	0.68
Calcium blocker (%)	48	42	0.65
Furosemide or bumetanide (%)	10	35	0.02*
Thiazide (%)	16	27	0.33
Biochemistry			
Lactate peak (mmol/l)	5.9 [4.6–7.6]	6.8 [4.1–8.2]	0.60
Creatinine (μmol/l)	99 [79–120]	122 [97–151]	0.02*
Hemoglobin (mmol/l)	8.7 [8–9.6]	8.2 [7.3–8.9]	0.02*
Troponin-T (ng/l)	5 [5–14]	16.5 [10–26]	0.01*
NT-ProBNP (ng/l)	304 [154–893]	501 [323–1064]	0.03*
Micro- and macrovascular dysfunction			
Graft vasculopathy (%)	39	65	0.046*
Previous PCI treatment (%)	13	23	0.32
Myocardial blood flow, rest (ml/g/min)	1.1 ± 0.3	1.2 ± 0.2	0.83
Myocardial blood flow, hyperemic (ml/g/min)	3.5 ± 1.1	2.9 ± 1.2	0.08
Coronary flow reserve (ratio)	3.1 ± 1.0	2.5 ± 1.0	0.06
Subgroup without present coronary stenosis >70%	n = 26	n = 16	
Myocardial blood flow, rest (ml/g/min)	1.1 ± 0.3	1.2 ± 0.3	0.71
Myocardial blood flow, hyperemic (ml/g/min)	3.7 ± 1.0	3.4 ± 1.0	0.43
Coronary flow reserve (ratio)	3.3 ± 1.0	3.0 ± 0.9	0.34

Data are presented as absolute number and present or mean ± standard deviation or median and IQR.
LV, left ventricle; NYHA, New York heart association; EMB, ndomyocardial biopsy; PCI, percutaneous coronary intervention; IQR, interquartile range.
*$P < 0.05$.

present coronary stenosis >70% were excluded (n = 15). After exclusion of these patients, we found no difference between the two groups concerning resting myocardial blood flow (P = 0.71), hyperemic myocardial blood flow (P = 0.43), or CFR (P = 0.34).

Resting hemodynamics

Echocardiographic and invasive hemodynamic parameters at rest are shown in Table 2. Traditional pulsed Doppler parameters of LV filling, E/A-ratio, and E-deceleration time did not differ significantly between the two groups, whereas left atrial volume was significantly larger ($P < 0.01$), E/e′-ratio significantly higher ($P < 0.001$), and IVRT significantly shorter (P = 0.01) in patients with elevated LV-FP than in patients with normal LV-FP.

All parameters of LV systolic function tended to be lower in patients with elevated LV-FP than in patients with normal LV-FP (2D-LVEF: P = 0.09; S′: $P < 0.01$; LV-GLS: P = 0.13). Three patients (5%) had LVEF < 45% at rest.

As expected, LV-FP and RV-FP were significantly higher in the group with elevated LV-FP than in the normal LV-FP group (PCWP: $P < 0.0001$; mRAP: $P < 0.001$; mPAP: $P < 0.001$). However, there was no difference in CI between the groups (CI: P = 1.00). Ten patients had resting PCWP ≥15 mmHg.

Table 2. Echocardiographic and hemodynamic parameters at rest.

	Normal LV filling pressure (n = 31)	Elevated LV filling pressure (n = 26)	P
2D echocardiography			
LV-mass (g/m^2)	83 ± 21	99 ± 41	0.11
LVEF Simpson biplane (%)	63 ± 9	59 ± 10	0.09
LV-EDV (ml)	87 ± 25	102 ± 34	0.05
LV-ESV (ml)	33 ± 14	44 ± 23	0.05
LV-S′ mean (cm/s)	6 ± 1	5 ± 1	0.001*
LV-GLS (%)	−15 ± 3	−14 ± 4	0.13
LA-volume (ml/m^2)	40 ± 12	53 ± 21	0.004*
E/A (ratio)	2.0 ± 0.6	2.2 ± 0.9	0.17
E-dec (msec)	167 ± 44	154 ± 54	0.33
IVRT (msec)	74 ± 24	59 ± 19	0.01*
E/e′ (ratio)	8 ± 3	13 ± 7	0.0001*
Hemodynamics			
SBP (mmHg)	133 ± 18	136 ± 19	0.61
MAP (mmHg)	102 ± 12	102 ± 12	0.87
HR (beats/min)	84 ± 12	84 ± 16	0.91
AV-diff (%)	28 ± 4	29 ± 6	0.39
SVRI (dynes * s * cm^{-5} *m^2))	2960 ± 495	2889 ± 609	0.63
CO (l/min)	5.2 ± 1.1	5.3 ± 1.0	0.54
CI (l/min/m^2)	2.7 ± 0.4	2.7 ± 0.4	1.00
CO*SvO$_2$ (l/min)	363 ± 86	367 ± 86	0.86
VO$_2$ (l/min)	268 ± 58	263 ± 48	0.74
Stroke volume (ml)	63 ± 16	65 ± 16	0.58
mRAP (mmHg)	3 ± 2	7 ± 3	0.0001*
mPAP (mmHg)	16 ± 4	21 ± 6	0.0002*
mPCWP (mmHg)	8 ± 2	14 ± 5	<0.0001*
PVRI (dynes * s * cm^{-5} *m^2)	260 ± 116	236 ± 97	0.40
PAC (ml/mmHg)	5.8 ± 2.5	5.3 ± 1.9	0.33

Data are presented as mean ± standard deviation.
LV, left ventricle; LVEF, left ventricle ejection fraction; LV-EDV, left ventricle end diastolic volume; LV-ESV, left ventricle end systolic volume; GLS, global longitudinal strain; LA, left atrium; E-dec, E-deceleration time; IVRT, isovolumetric relaxation time; SBP, systolic blood pressure; MAP, mean arterial blood pressure; HR, heart rate; AV-diff, arterial-venous saturation difference; SVRI, systemic vascular resistance index; CO, cardiac output; CI, cardiac index; SvO2, mixed venous oxygen saturation; VO2, oxygen consumption; mRAP, mean right atrial pressure; mPAP, mean pulmonary arterial pressure; mPCWP, mean pulmonary capillary wedge pressure; PVRI, pulmonary vascular resistance index; PAC, pulmonary arterial compliance.
*$P < 0.05$.

Table 3. Echocardiographic and hemodynamic parameters at peak exercise.

	Normal LV filling pressure (n = 31)	Elevated LV filling pressure (n = 26)	P
Peak exercise (watt)	98 ± 39	90 ± 36	0.48
2D echocardiography			
LVEF Simpson biplane (%)	70 ± 8	66 ± 11	0.07
LV-EDV (ml)	90 ± 21	105 ± 31	0.09
LV-ESV (ml)	27 ± 10	37 ± 21	0.08
LV-S′ mean (cm/s)	9 ± 2	7 ± 2	0.004*
LV-GLS (%)	−19 ± 5	−16 ± 6	0.01*
E/A (ratio)	1.8 ± 0.8	2.5 ± 1.5	0.04*
E-dec (msec)	112 ± 36	89 ± 27	0.01*
IVRT (msec)	30 ± 14	20 ± 11	0.01*
E/e′ (ratio)	10 ± 3	14 ± 6	0.0003*
Hemodynamics			
SBP (mmHg)	199 ± 27	198 ± 35	0.91
MAP (mmHg)	127 ± 12.2	129 ± 20	0.85
HR (beats/min)	132 ± 13	132 ± 20	0.96
AV-diff (%)	65 ± 11	69 ± 10	0.17
SVRI (dynes * s * cm^{-5} *m^2)	1650 ± 446	1563 ± 499	0.56
CO (l/min)	12.0 ± 3.8	11.3 ± 3.6	0.44
CI (l/min/m^2)	6.3 ± 1.6	5.7 ± 1.6	0.18
CO*SvO$_2$ (l/min)	362 ± 122	293 ± 139	0.06
VO$_2$ (l/min)	1470 ± 588	1351 ± 509	0.45
Stroke volume (ml)	91 ± 26	86 ± 25	0.51
mRAP (mmHg)	11 ± 6	19 ± 9	0.002*
mPAP (mmHg)	32 ± 6	41 ± 6	<0.0001*
mPCWP (mmHg)	18 ± 4	34 ± 4	<0.0001*
TPG (mmHg)	14 ± 5	8 ± 4	0.0002*
PVRI (dynes * s * cm^{-5} *m^2)	192 ± 100	131 ± 83	0.02*
PAC (ml/mmHg)	5.8 ± 4.1	3.6 ± 1.6	0.004*

Data are presented as mean ± standard deviation.
LV, left ventricle; LVEF, left ventricle ejection fraction; LV-EDV, left ventricle end diastolic volume; LV-ESV, left ventricle end systolic volume; GLS, global longitudinal strain; LA, left atrium; E-dec, E-deceleration time; IVRT, isovolumetric relaxation time; SBP, systolic blood pressure; MAP, mean arterial blood pressure; HR, heart rate; AV-diff, arterial–venous saturation difference; SVRI, systemic vascular resistance index; CO, cardiac output; CI, cardiac index; SvO2, mixed venous oxygen saturation; VO2, oxygen consumption; mRAP, mean right atrial pressure; mPAP, mean pulmonary arterial pressure; mPCWP, mean pulmonary capillary wedge pressure; TPG, transpulmonary gradient; PVRI, pulmonary vascular resistance index; PAC, pulmonary arterial compliance.
*$P < 0.05$.

Exercise hemodynamics

All patients exercised to exhaustion defined as >18 on the Borg scale. Peak workload ($P = 0.48$) and peak lactate ($P = 0.60$) did not differ between the two groups.

Echocardiographic and invasive hemodynamic responses to exercise are shown in Table 3. Patients with elevated LV-FP had lower peak exercise values of E-deceleration time ($P = 0.01$) and IVRT ($P < 0.01$) and higher E/e′-ratio ($P < 0.001$) than patients with normal LV-FP. However, the change from baseline to peak exercise did not differ between the two groups. LV systolic function was augmented by exercise in both groups, but we found

Figure 1 Functional and hemodynamic response to exercise in patients with and without elevated left ventricular filling pressure (LV-FP). a & b: Box plots and *t*-test analysis. Each box plot shows the mean ± standard deviation. (a) Change in left ventricular ejection fraction (LVEF) from rest to peak exercise. (b) Change in left ventricular global longitudinal strain (LVGLS) from rest to peak exercise. (c) & (d) Margins plot with 95% confidence interval. (c) Pulmonary capillary wedge pressure (PCWP) increased more in the patients with elevated LV filling pressure than in patients with normal LV filling pressure. *$P < 0.05$. (d) ΔPCWP increased more in patients with elevated LV filling pressure than in patients with normal LV filling pressure. *$P < 0.05$.

significantly higher S′ velocities ($P < 0.01$) and LV-GLS ($P = 0.01$) in patients with normal LV-FP than in patients with elevated LV-FP. It is noteworthy that neither the increase in LVEF during exercise ($P = 0.84$) nor the peak exercise LVEF ($P = 0.07$) differed significantly between the groups (Fig. 1 a and b).

As expected, LV-FP (ΔmPCWP = 20 ± 6 mmHg vs. 11 ± 4 mmHg, $P < 0.0001$), RV-FP (ΔRAP; 12 ± 8 mmHg vs. 7 ± 5 mmHg, $P < 0.001$), and PA pressures (ΔmPAP 20 ± 6 mmHg vs. 16 ± 5 mmHg, $P < 0.01$) increased more in patients with elevated LV-FP than in patients with normal LV-FP (Fig. 1c and d).

The PCWP/watt ratio was significantly higher in patients with elevated LV-FP than in patients with normal LV-FP: 0.4 ± 0.3 mmHg/watt vs. 0.2 ± 0.1 mmHg/watt ($P < 0.0001$). We found a good correlation between PCWP/watt and peak exercise cardiac index ($R = -0.49$, $P < 0.0001$) (Fig. 2). In patients with elevated LV-FP, PAC was significantly lower and decreased during exercise leading to lower PAC at peak exercise than in patients with normal LV-FP ($P < 0.01$). No significant differences were seen in changes of cardiac index and stroke volume when the groups were compared during exercise (ΔCI: $P = 0.15$, ΔSV: $P = 0.56$).

Determinants of elevated LV-FP

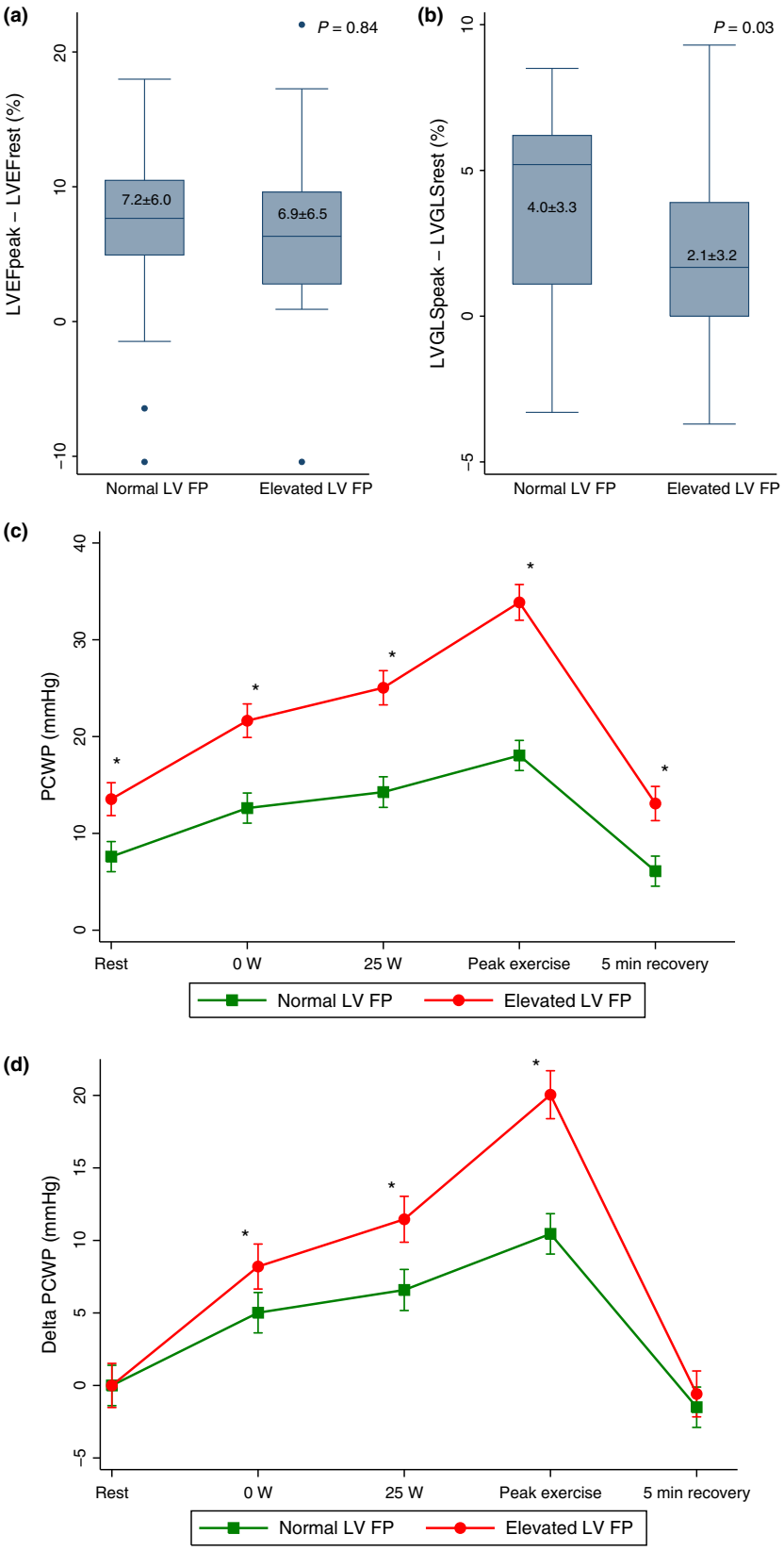
Clinical and hemodynamic parameters associated with elevated LV-FP are shown in Table 4. Time since transplantation, CAV, renal dysfunction, hemoglobin, and previous moderate/severe rejection episodes were all predictors of elevated LV-FP at rest and/or during exercise. After adjustment of time since transplantation, number of previous moderate/severe rejections (odds ratio 3.3 pr 2R rejection episode, 95% CI 1.1–7.9, $P < 0.01$) and hemoglobin (odds ratio 0.47 pr mmol/l hemoglobin, 95% CI 0.25–0.88, $P < 0.05$) remained significantly correlated with the presence of elevated LV-FP. In contrast, the presence of CAV (odds ratio 2.19, 95% CI 0.68–7.07, $P = 0.19$) and renal dysfunction (odds ratio 1.01 pr μmol/l creatinine, 95% CI 1.00–1.03, $P = 0.07$) was not significantly correlated with the presence of elevated LV-FP after time since transplant adjustment. We found that exercise E/e′-ratio, peak exercise LV-GLS, peak exercise S′, and PAC were significantly correlated with the presence of elevated LV-FP.

Elevated LV-FP with and without CAV

In the subgroup analysis where patients with and without CAV were compared, 11 patients (41%) with elevated LV-FP had CAV (ISHLT class 2 or 3), and 15 patients (59%) with elevated LV-FP did not have CAV. Patients with both elevated LV-FP and CAV were more symptomatic (NYHA functional class >1 72% vs. 20%, $P < 0.01$), had reduced CFR (1.7 ± 0.7 vs. 3.1 ± 0.9, $P = 0.0001$), decreased LV systolic deformation capacity during exercise (peak exercise LV-GLS −11 ± 6% vs. −19 ± 4%, $P < 0.001$), and lower CI (4.9 ± 1.0 l/min/m^2 vs. 6.2 ± 1.8 l/min/m^2, $P < 0.05$) than patients without CAV. No difference was seen in previous number of rejection episodes demanding treatment with CAV group: 1.0 ± 0.9 ≥ 2R rejection episodes versus without CAV group: 1.5 ± 1.6 ≥ 2R rejection episodes ($P = 0.38$). Furthermore, no difference was observed between the groups in peak exercise workload (with CAV group: 79 ± 29 W versus without CAV group: 98 ± 39 W, $P = 0.20$).

Discussion

The present study is, to our knowledge, the most comprehensive study of the hemodynamic and graft function response to exercise in HTX patients. Our study demonstrates that elevated LV-FP is common (46%) in stable HTX patients with an average graft age exceeding 9 years. From a clinical perspective, patients with elevated LV-FP were more symptomatic, had experienced more previous rejections, and had higher graft age, and CAV was more frequently present than in patients with normal LV-FP. At rest, traditional echocardiographic and invasive measurements of systolic myocardial function, such as fractional shortening, LVEF, CI, and SV, were within the normal range and did not differ between the two groups. Similarly, at peak exercise, LVEF, CI, and SV were comparable between the two groups. However, markers of LV long-axis systolic function were significantly lower as LV-FP increased further and LV filling pattern was more Doppler-restrictive in the elevated LV-FP group during exercise than in the normal LV-FP group. Only 38% (10/26) of patients with elevated LV-FP had resting PCWP >15 mmHg. This finding is similar to the finding by Meluzin *et al.* [7] in an HTX population with preserved LVEF. This similarity emphasizes that the assessment of elevated LV-FP during


(a)
P = 0.84
LVEFpeak – LVEFrest (%)
20
10
0
−10
7.2±6.0
6.9±6.5
Normal LV FP
Elevated LV FP
(b)
P = 0.03
LVGLSpeak – LVGLSrest (%)
10
5
0
−5
4.0±3.3
2.1±3.2
Normal LV FP
Elevated LV FP
(c)
PCWP (mmHg)
40
30
20
10
0
*
Rest
0 W
25 W
Peak exercise
5 min recovery
Normal LV FP
Elevated LV FP
(d)
Delta PCWP (mmHg)
20
15
10
5
0
−5
*
Rest
0 W
25 W
Peak exercise
5 min recovery
Normal LV FP
Elevated LV FP

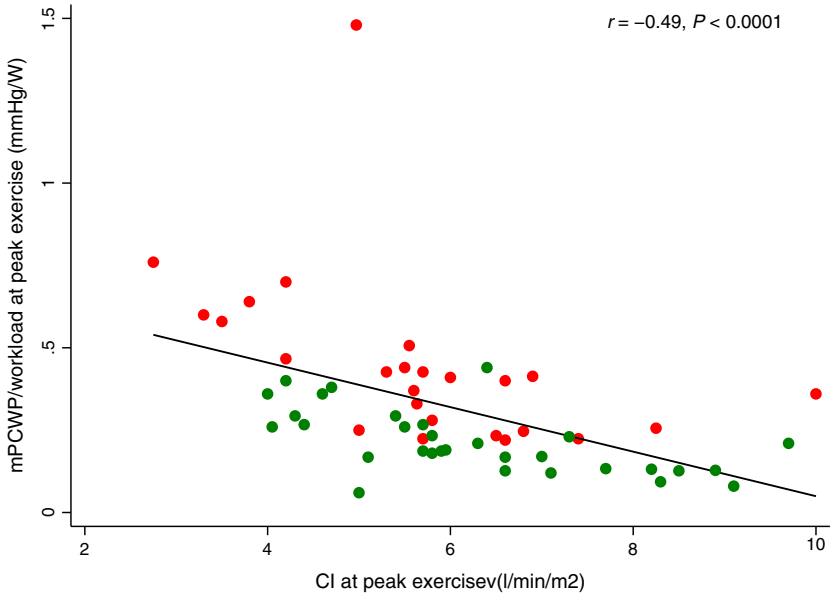


Figure 2 Scatter plots with regression lines for peak exercise cardiac index (CI) and peak exercise pulmonary capillary wedge pressure (PCWP)/watt. Demonstrated *r* and *P* value for combined normal and elevated left ventricular filling pressure groups. Red circles = elevated left ventricular filling pressure group: β_0 = 0.9 (95% CI 0.6:1.2) β_1 = −0.08(95% CI −0.12: −0.04). Green circles = normal left ventricular filling pressure group. β_0 = 0.4 (95% CI 0.2:0.7) β_1 = −0.04(95% CI −0.08:0.00).

Table 4. Determinants of elevated left ventricular filling pressure.

	Univariate	
	Odds ratio (95% CI)	*P*-value
Donor age	1.01 (0.96–1.06)	0.78
Age	1.02 (0.98–1.06)	0.39
Time since transplantation	1.10 (1.00–1.20)	0.047*
BMI	1.02 (0.90–1.16)	0.71
Diabetes	1.56 (0.42–5.85)	0.51
Hypertension	0.81 (0.18–3.63)	0.79
Hemoglobin	0.51 (0.28–0.91)	0.02*
Creatinine	1.02 (1.00–1.03)	0.03*
Number of EMBs showing ≥2R	2.97 (1.36–6.50)	0.01*
Graft vasculopathy	2.99 (1.01–8.84)	0.048*
Coronary flow reserve	0.58 (0.33–1.04)	0.07
Peak exercise PAC	0.67 (0.46–0.97)	0.03*
Peak exercise S'	0.68 (0.51–0.91)	0.01*
Peak exercise LV-GLS	0.89 (0.79–0.98)	0.02*
Peak exercise LVEF	0.95 (0.89–1.01)	0.08

BMI, body mass index; EMB, endomyocardial biopsy; PAC, pulmonary arterial compliance; S', *peak systolic* mitral annular velocities; LV, left ventricle; GLS, global longitudinal strain; LVEF, left ventricle ejection fraction.
*$P < 0.05$.

resting conditions falls short as a measure for evaluating myocardial systolic and diastolic performance. Exercise testing should therefore be performed when assessing the hemodynamics of these patients as also recommended in patients with heart failure with preserved LVEF [34].

Despite preserved LVEF, long-axis systolic function assessed by LV-S' and LV-GLS was significantly impaired in patients with elevated LV-FP compared with patients with normal LV-FP at peak exercise. This indicates that both the systolic and the diastolic capacity seem to be impaired in patients with elevated LV-FP. The relation between systolic and diastolic myocardial capacity was supported by a strong correlation between PCWP/watt and CI during exercise. This indicates that an increase in the preload in the elevated LV-FP group may be a compensatory mechanism that serves to maintain adequate CI despite impaired long-axis function. The systolic long-axis function predominantly represents the function of the longitudinally oriented subendocardial myocardial fibers, which are very sensitive to ischemia, edema, and fibrosis [35]. For the assessment of CAV-induced graft dysfunction, 2D speckle tracking echocardiographic assessment of LV longitudinal myocardial deformation has been shown to outperform traditional parameters such as fractional shortening, LVEF, and tissue Doppler velocities [36]. However, in the present study, we found impaired longitudinal myocardial systolic capacity only in patients with elevated LV-FP in combination with severe CAV.

In the CAV classification by the ISHLT, signs of elevated LV-FP or restrictive LV filling pattern indicate severe CAV [30]. Conversely, the link between CAV and elevated LV-FP has not been established and, furthermore, echocardiographic diastolic Doppler assessment of the mitral flow pat-

tern correlates poorly with angiographically assessed CAV [36]. In the present study, elevated LV-FP was most common in patients without severe CAV, and we found only a trend toward a higher prevalence of severe CAV in patients with elevated LV-FP than in patients with normal LV-FP. Additionally, after excluding patients with severe coronary stenosis, we found no difference in CFR when the two groups were compared. Consistent with this finding, Haddad *et al.* [37] found no correlation between an index of microcirculatory resistance and LV or RV filling pressure.

It is noteworthy that the patients with elevated LV-FP and no significant CAV had a significantly higher rejection burden than patients with normal LV-FP. This is interesting; until today, histological studies found no link between rejection burden and the development of interstitial myocardial fibrosis [5,6,38]. On the other hand, patients with severe or repeated rejection episodes may have received higher doses of immunosuppressive treatment in periods after heart transplantation, which is associated with myocardial fibrosis [6,38]. In addition, a high rejection burden is associated with a significantly reduced longitudinal myocardial deformation [39], microvascular CAV [40], and macrovascular CAV [33], all of which potentially could influence LV filling.

We did not evaluate the prognostic implication of elevated LV-FP in the present study; still, we found a higher prevalence of surrogate markers of inferior prognosis such as elevated NT-proBNP [41] and troponin-T [42,43], anemia, renal dysfunction [44], and higher NYHA functional class in patients with elevated LV-FP than in patients with normal LV-FP.

Limitation

We acknowledge a number of limitations to this study. It reflects the experience of a single center with a relatively small cohort of patients, and we did not evaluate the degree of myocardial fibrosis. Hemodynamic assessment can be challenging during exercise due to respiratory and cardiac motion; hence, only experienced senior consultants with expertise in hemodynamics performed the invasive measurements during exercise tests.

Conclusions

Direct, invasive measurement of LV filling at rest and during exercise identified elevated LV-FP in approximately 50% of HTX patients. Despite preserved CI and LVEF, patients with elevated LV-FP showed significantly reduced LV longitudinal myocardial deformation capacity, were more symptomatic, had higher rejection burden, and had higher serum levels of NT-ProBNP and troponin-T. We therefore suggest exercise stress test with the assessment of longitudinal myocardial deformation capacity considered in routine surveillance of long-term HTX patients as a marker of restrictive filling.

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