

Right ventricular hemodynamics and performance in relation to perfusion during first year after heart transplantation

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Abstract

Aims We aim to evaluate changes in invasive haemodynamics, right ventricular (RV) function, and perfusion during the first year after heart transplantation (HTx) and to determine the relation between RV function and myocardial perfusion.

Methods and results Thirty patients were prospectively enrolled at the time of HTx. Right heart catheterization (RHC), comprehensive 2D and 3D echocardiography and cardiac biomarkers were performed at baseline (≤ 2 weeks after HTx) and at follow-up 1, 3, 6, and 12 months after HTx. At 12 months, HTx patients were subjected to an exercise stress test with assessment of maximal oxygen consumption (VO_2max). RV myocardial perfusion reserve was evaluated by ^{15}O - H_2O positron emission tomography at baseline and at 3 and 12 months after HTx. A group of 43 healthy subjects served as echocardiographic controls and a subgroup comprising 16 healthy controls underwent exercise stress test with simultaneous RHC. At baseline, HTx patients had higher pulmonary artery wedge pressure (PAWP) and right atrial pressure (RAP) and pulmonary vascular resistance (PVR) than healthy controls whereas cardiac index (CI) was reduced (PAWP: 14 mmHg [8;17] vs. 8 mmHg [7;10]; RAP: 7 mmHg [4;11] vs. 5 mmHg [4;6]; PVR: 1.9 wood units [1.3;2.6] vs. 1.1 wood units [1.0;1.4]; CI 2.4 L/min/m² [2.2;2.8] vs. 3.3 L/min/m² [2.8;3.6], all $P < 0.05$). Normalization of filling pressures and CI was seen 3–6 months after HTx. During follow-up, RV function in terms of 3D ejection fraction (EF) and longitudinal strain (LS) improved in HTx patients but remained reduced compared with healthy controls at 12 months follow-up (3D RV EF: 52 \pm 7% vs. 60 \pm 8%; RV LS: 22 \pm 4% vs. 28 \pm 5%, both $P < 0.001$). During follow-up, RV perfusion reserve improved (baseline 2.1 \pm 0.9; 3 months follow-up 3.2 \pm 0.8; 12 months follow-up 3.7 \pm 1.1, $P < 0.0001$). RV perfusion reserve significantly correlated to cardiac markers in terms of troponin T ($r = -0.62$, $P < 0.0001$), NT-proBNP ($r = -0.65$, $P < 0.0001$), RAP ($r = -0.43$, $P < 0.01$) and CI ($r = 0.37$, $P < 0.01$) and with VO_2max 12 months after HTx ($r = 0.75$, $P < 0.01$).

Conclusions Normalization of left and right atrial filling pressures is demonstrated within the first 3 to 6 months after HTx. RV function and RV perfusion reserve correlated and gradually improved during the first year after HTx but RV function remained reduced in HTx patients compared with healthy controls.

Keywords Heart transplantation; Right ventricular function; Haemodynamics; Myocardial perfusion; Echocardiography

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Introduction

Early right ventricular (RV) failure is a serious and feared complication following heart transplantation (HTx) and accounts for approximately 50% of all early complications and

approximately 19% of early deaths.^{1–4} Pre-transplant elevated pulmonary vascular resistance (PVR), prolonged ischaemic time, high donor age, and gender mismatch are identified as the most important risk factors for early RV failure.^{5–7} After HTx, the donor heart adapts to the altered pulmonary

and systemic loading conditions with improvements of both left and right ventricular function.⁸ However, RV function and exercise capacity remain reduced compared with healthy individuals.^{7,9} Changes in loading conditions during the first post-operative year and the relation to RV function assessed by invasive haemodynamics, and advanced 2D and 3D echocardiography have not been systematically reported. Myocardial function is highly dependent on myocardial perfusion. The latter can be assessed by advanced ¹⁵O-H₂O positron emission tomography (PET). However, changes in RV perfusion reserve and relation to RV function have not been evaluated in HTx patients.

Thus, the aims of this study were to evaluate changes in invasive haemodynamics and RV function during the first year in consecutive de novo HTx patients and to determine the relation between RV function and RV perfusion.

Methods

Study population

The study population comprised of 30 patients prospectively enrolled at the time of HTx. During follow-up, three patients died and one patient withdrew consent. Thus, a total of 26 patients completed the study program. A group of 43 healthy subjects served as controls for echocardiographic RV functional assessment. Of these, 16 subjects underwent right heart catheterization (RHC) and an exercise stress test with assessment of maximal oxygen consumption (VO₂).

The study program for the HTx patients encompassed five visits; baseline (≤ 2 weeks after HTx) and follow-up (1, 3, 6, and 12 months after HTx). At each visit, all patients underwent advanced 2D and 3D evaluation of left ventricular (LV) and RV function, invasive RHC, endomyocardial biopsy, and measurements of troponin T and N-terminal pro-brain natriuretic peptide (NT-ProBNP). A ¹⁵O-H₂O PET was performed at baseline and 3 and 12 months after HTx. Coronary angiogram (CAG) was performed 3 and 12 months after HTx. Finally, a cardio-pulmonary exercise stress test with assessment of maximal VO₂ was performed 12 months after HTx.

Patients ≥ 18 years of age were included after written informed consent according to the principles of the Declaration of Helsinki. The healthy controls received no medication and had no cardio-pulmonary symptoms. The study was approved by the local scientific ethical committee of the Central Denmark Region and registered with ClinicalTrials.gov (NCT02077764).

Data from the present study-cohort have been used partly in a previous paper describing development of CAV after HTx.¹⁰

Invasive haemodynamic

Right heart catheterization was performed using a standard 7.5-F triple lumen Swan-Ganz thermistor and balloon-tipped catheter (Edwards Lifesciences, Irvine, California, USA). The catheter was introduced into the right jugular or femoral vein using ultrasound guidance and advanced using pressure waveform and fluoroscopy guidance into the pulmonary artery (PA). Pulmonary artery wedge pressure (PAWP), mean right atrial pressure (mRAP), systolic and diastolic PA pressure (sPAP, dPAP), mean PA pressure (mPAP), and central oxygenation were measured. Finally, we measured cardiac output (CO) by thermodilution as an average of three measurements with $< 10\%$ difference.

Echocardiography

Echocardiography was performed using a commercially available ultrasound system (Vivid 9, GE Healthcare Horten, Norway) with a 3.5-MHz-phased array transducer (M5S) for 2D evaluation and a 4 V-D transducer for 3D evaluation.

At each study visit, patients and controls underwent a comprehensive 2D and 3D echocardiographic assessment according to current guidelines.¹¹ RV free-wall-GLS (RV-FW-LS) was assessed from a modified four-chamber view with a frame rate > 55 frames/s averaging the three lateral segments. The region of interest was manually adjusted for optimal tracking results. We measured 3D RV-EF by sampling six heartbeats during breath-hold aiming at a frame rate > 25 frames/s.

Data were analysed offline using dedicated software (EchoPAC PC SW-Only, 113, GE-Healthcare, Milwaukee, Wisconsin, USA and TomTec 4D RV-function, Munich, Germany) by a single investigator (T. S. C.) blinded to clinical status and invasive measurements.

¹⁵O-H₂O positron emission tomography

The safety of adenosine was tested by bedside adenosine challenge. If the patient developed advanced AV block, sinus block > 3 s, or unacceptable side effects, the patient was not subjected to PET scan. The PET scans were performed both at rest and adenosine-induced hyperaemic conditions using Siemens Biograph 64 TruePoint TrueV PET/CT (Siemens Healthcare, Erlangen, Germany). All subjects were instructed to avoid caffeine-containing drinks for 24 h before testing.

A low-dose CT scan was performed for attenuation correction. Afterwards, a list-mode resting emission scan was conducted with simultaneous automated bolus injection of 400 MBq of ¹⁵O-H₂O followed by a 20 mL saline flush. The stress scan was initiated at the time of a second injection of 400 MBq of ¹⁵O-H₂O followed by a 20 mL saline flush. The adenosine infusion (140 μ g/kg/min) was initiated 2 min

before the stress scan and continued for the 6 min PET-scan. Emission data were reconstructed into a dynamic scan consisting of 22 time frames with a matrix size of $4 \times 4 \times 4$ mm per frame using the TrueX reconstruction algorithm. The data were analysed by a single blinded viewer (HH) using aQuant Research Software. Resting and hyperaemic myocardial blood flow of both LV and RV were obtained. The RV perfusion reserve was calculated as the ratio of hyperaemic to resting myocardial blood flow.

Statistics

Normally distributed data are presented as mean \pm standard deviation (SD); non-normally distributed data are presented as median and interquartile range [IQR]. Categorical data are presented as absolute values with percentages. Histograms and Q-Q plots were used to check continuous values for normality of the data distribution. Between-group differences were assessed by mixed model ANOVA, Student's *t*-test, or Wilcoxon rank test, as appropriate.

A linear regression model was used to compare continuous variables, and predicted value and residual were used to check the regression models.

$P < 0.05$ was considered statistically significant. Analyses were performed using STATA (STATA/IC 13, StataCorp LP, Texas, College Station, USA).

Results

Demographics and serological adaption

Demographics of the HTx patients and healthy controls are displayed in *Table 1*. The HTx group and control group did not differ in age. The majority of HTx patients were transplanted due to cardiomyopathy. The mean donor age was 45 years and cold ischaemic time approximately 3 h.

During follow-up, the prevalence of hypertension increased, and we noted a stepwise improvement in renal function, and a decline in NT-ProBNP and Troponin T. Interestingly, the improvement in biomarkers continued between 6 and 12 months after HTx despite stable renal function. Furthermore, both NT-ProBNP and Troponin T were higher in HTx patients at 12 months follow-up compared with healthy controls. The changes in NT-ProBNP and Troponin T during the first year after HTx are illustrated in *Figure 1*. Patients who had at least

Table 1 Patient characteristics

	Baseline (N = 29)	12 months follow-up (N = 26)	Controls (N = 43)	P-value
Demographics				
Men (%)	24 (83)	21 (81)	25 (58)	<0.05 ^b
Age at baseline (years)	53 \pm 13	-	51 \pm 11	0.74 ^b
Reason for HTx				
Cardiomyopathy, n (%)	15 (52)	-	-	-
Ischaemic heart disease, n (%)	8 (28)	-	-	-
Other, n (%)	6 (21)	-	-	-
Cold ischaemic time (min)	182 \pm 50	-	-	-
Donor age (years)	45 \pm 12	-	-	-
Diabetes (%)	7 (24)	3 (12)	0	0.23 ^a
Hypertension (%)	9 (31)	19 (73)	0	0.002 ^a
Medication				
Prednisolone (%)	29 (100)	26 (100)	0	- ^a
Ciclosporine (%)	0 (0)	1 (4)	0	0.29 ^a
Tacrolimus (%)	29 (100)	24 (92)	0	0.13 ^a
Everolimus (%)	0 (0)	2 (8)	0	0.13 ^a
Mycophenolate (%)	29 (100)	26 (100)	0	- ^a
Statins (%)	23 (79)	23 (88)	0	0.36 ^a
ACE/AT II inhibitor (%)	6 (21)	17 (65)	0	0.001 ^a
Loop diuretics (%)	25 (86)	6 (23)	0	<0.0001 ^a
Calcium channel blocker (%)	5 (17)	7 (27)	0	0.39 ^a
Aspirin (%)	3 (10)	3 (12)	0	0.89 ^a
Biochemistry				
Creatinine (μ mol/L)	107 [95;137]	89 [77;110]	76 [70;86]	<0.0001 ^b
Haemoglobin (mmol/L)	6.1 [5.8;6.6]	8.0 [7.3;8.5]	9.1 [8.5;9.5]	<0.0001 ^b
Total cholesterol (mmol/L)	3.4 [3.0;3.9]	5.1 [4.2;5.4]	4.6 [4.0;5.4]	<0.0001 ^b
Troponin-T (ng/L)	556 [330;868]	12 [6;16]	6 [6;6]	<0.0001 ^b
NT-ProBNP (ng/L)	5,782 [3,401;7,922]	252 [156;474]	37 [34;96]	<0.0001 ^b
VO ₂ max (mL/kg/min)	-	20 [18;22]	34 [30;42]	<0.0001 ^b

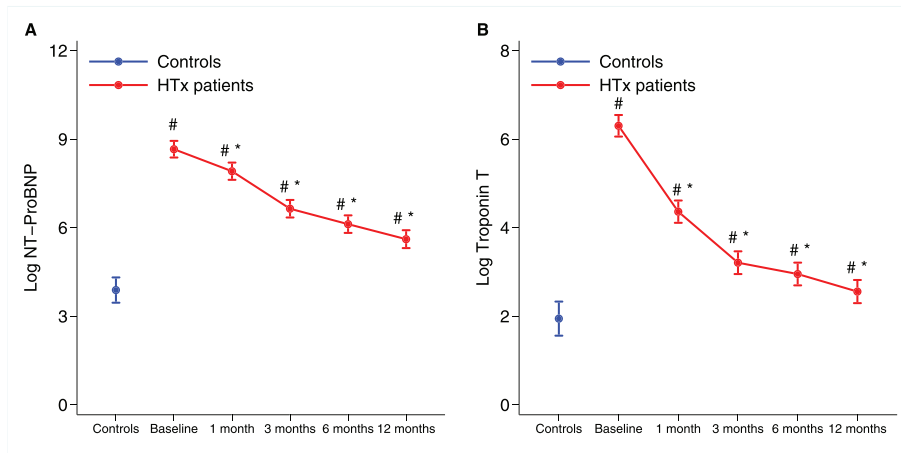
Data are presented as absolute number and present or mean \pm standard deviation or median and IQR.

IQR, interquartile range; ACE, angiotensin converting enzyme; AT, angiotensin; NT-ProBNP, N-terminal pro-brain natriuretic peptide; VO₂max, maximal oxygen consumption.

^aTesting baseline versus follow-up.

^bANOVA test of difference between all three groups.

Figure 1 Margin plots with 95% confidence intervals (bars) during follow-up in reference to the logarithmic value of NT-ProBNP and Troponin T. *Significant difference compared with baseline value ($P < 0.05$). #Significant difference between HTx patients and controls ($P < 0.05$).



one treatment demanding acute cellular rejection grade $\geq 2R$ ($n = 11$) had higher average levels of Troponin T (54 ng/L [19;168] vs. 25 ng/L [13;116], $P < 0.05$) and NT-ProBNP (1557 ng/L [496;3,050] vs. 678 ng/L [326;2,451], $P < 0.05$) than patients without rejections ($n = 15$) during 12 months follow-up. If we excluded the baseline values likely affected to the surgical trauma, the optimal cut-off points to differentiate patients with and without rejection during follow-up were: Troponin T: 28 ng/L (sensitivity 0.57 and specificity 61%, AUC 0.63 (0.52;0.74)); NT-ProBNP: 665 ng/L (sensitivity and specificity both 61%, AUC 0.61 (0.51;0.72)).

Invasively assessed haemodynamic alterations during first year post-heart transplantation

Changes in haemodynamic parameters of left and right heart filling pressures are illustrated in *Figure 2*. At baseline, HTx patients had higher left and right heart filling pressures and PVR than healthy controls. Furthermore, the cardiac index was significantly reduced. Normalization of filling pressures and cardiac index was observed between 3 and 6 months after HTx. However, the PVR remained slightly higher in the HTx group compared with healthy controls. We observed no significant differences in the haemodynamic adaptation between patients with or without treatment demanding rejection during follow-up.

Serial assessment of right ventricular function by 2D-and 3D echocardiography

Changes in RV systolic parameters are illustrated in *Figure 3*. During follow-up, all parameters of systolic RV function

improved but remained reduced compared with healthy controls. Thus, at 12 months follow-up, tricuspid annular plane systolic excursion (TAPSE) was 44% lower in HTx patients than healthy controls, 3D RV-EF was 13% lower in HTx patients than healthy controls and RV-FW-LS was 21% lower in HTx patients than controls. At 12 months follow-up, only nine of 26 patients (35%) had TAPSE (>17 mm), 3D RV-EF ($>45\%$), and RV-FW-LS ($<-20\%$) within normal range, and only 14 of 26 patients (54%) had TAPSE >1.4 cm. 3D RV-EF and RV-FW-LS both stabilized 1 month after HTx. In contrast, TAPSE continued to improve during 12 months follow-up.

We observed no significant differences in TAPSE, 3D RV-EF, and RV-FW-LS between patients with or without treatment demanding rejection during follow-up. In HTx patients, weak correlations were seen between PVR and TAPSE ($R = -0.33$, $P < 0.0001$), 3D RV-EF ($R = -0.29$, $P = 0.001$), and RV-FW-LS ($R = -0.14$, $P = 0.09$).

Tricuspid annular plane systolic excursion poorly correlated with RV stroke work ($r = 0.12$, $P = 0.29$). However, afterload adjusted TAPSE in terms of TAPSE \times tricuspid regurgitation gradient was significantly correlated with RV stroke work ($r = 0.33$, $P < 0.01$). Similarly, TAPSE/mPAP significantly correlated with RV stroke work ($r = -0.21$, $P < 0.01$).

Changes of microvascular and macrovascular function

A total of 21 HTx patients were subjected to baseline $^{15}\text{O-H}_2\text{O}$ PET evaluation, and 17 of 21 patients were subjected to PET evaluation during follow-up. The $^{15}\text{O-H}_2\text{O}$ PET data are displayed in *Table 2*. We noted a gradual improvement of

Figure 2 Margin plots with 95% confidence intervals (bars) during follow-up in reference to (A) mean right atrial pressure; (B) mean pulmonary artery pressure; (C) mean capillary wedge pressure; (D) pulmonary vascular resistance; (E) right ventricular stroke work; (F) cardiac index. *Significant difference compared with baseline value ($P < 0.05$). #Significant difference between HTx patients and controls ($P < 0.05$).

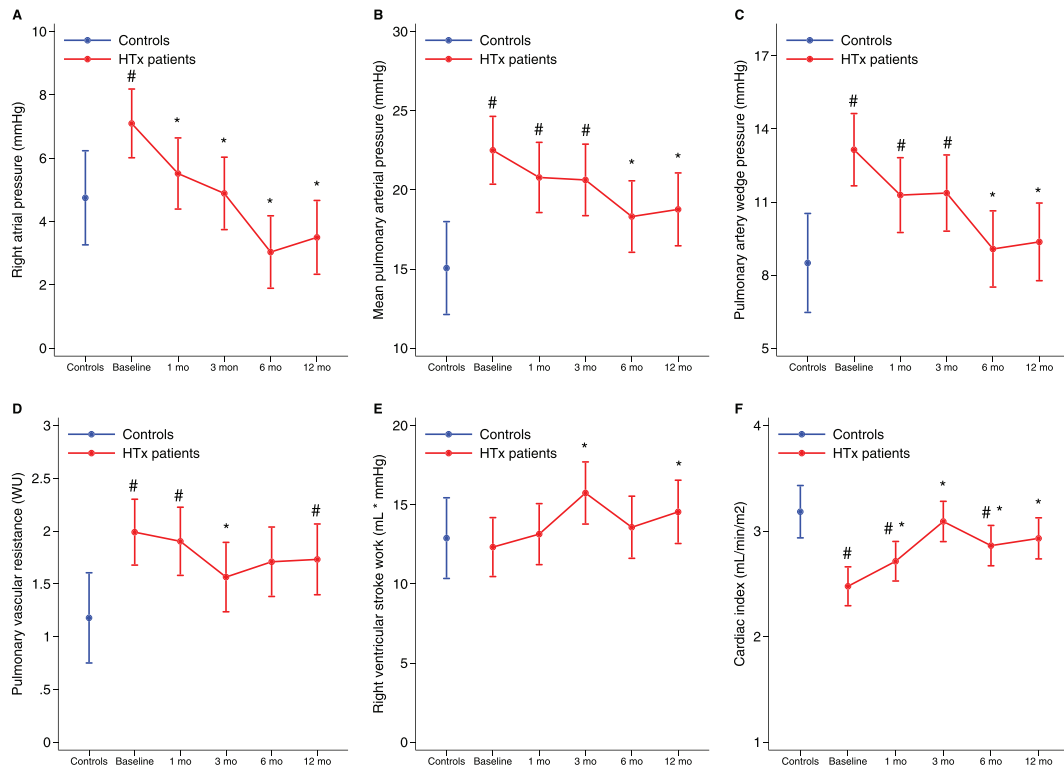
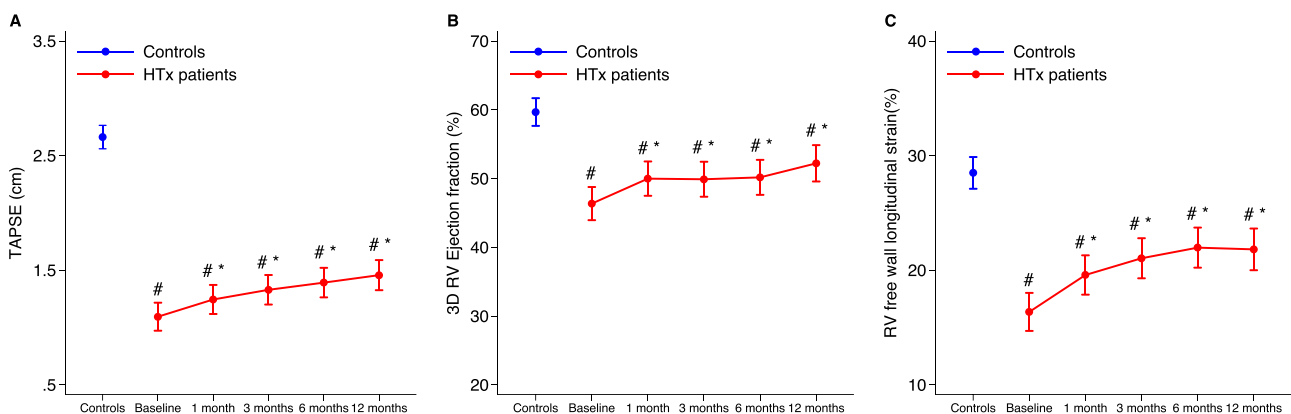


Figure 3 Margin plots with 95% confidence intervals (bars) during follow-up in reference to (A) tricuspid annular plane systolic excursion (TAPSE); (B) right ventricular (RV) ejection fraction by full volume 3D echocardiography; (C) RV free wall longitudinal strain. *Significant difference compared to baseline value ($P < 0.05$). #Significant difference between HTx patients and controls ($P < 0.05$).



RV myocardial perfusion reserve during follow-up. The improvement was primarily mediated by a reduction in resting RV myocardial blood flow. Patients who experienced at least one treatment demanding rejection during follow-up tended

to have lower average RV perfusion reserve than patients without rejection (2.9 ± 1.3 vs. 3.7 ± 1.7 , $P = 0.07$).

We noted a strong relation between RV perfusion reserve and LV perfusion reserve ($R = 0.84$, $P < 0.0001$).

Table 2 Left and right ventricular myocardial perfusion by ¹⁵O-H₂O positron emission tomography

	Baseline (N = 21)	3 months (N = 17)	12 months (N = 17)	ANOVA (P-value)
Rest				
LV myocardial blood flow (mL/g/min)	1.3 ± 0.3	1.2 ± 0.4	1.0 ± 0.3	<0.01
RV myocardial blood flow (mL/g/min)	0.9 ± 0.2	0.7 ± 0.2	0.6 ± 0.1	<0.0001
Stress conditions				
LV myocardial blood flow (mL/g/min)	2.6 ± 0.6	3.7 ± 1.5	3.6 ± 1.4	<0.01
RV myocardial blood flow (mL/g/min)	2.1 ± 0.7	2.7 ± 1.4	2.8 ± 1.0	0.05
Myocardial perfusion reserve				
LV myocardial perfusion reserve (ratio)	2.1 ± 0.9	3.2 ± 0.8	3.7 ± 1.1	<0.0001
RV myocardial perfusion reserve (ratio)	2.4 ± 1.0	3.7 ± 1.7	4.5 ± 1.5	<0.0001
LV/RV perfusion ratio	0.9 ± 0.2	1.0 ± 0.3	0.8 ± 0.2	0.11

Data are presented as mean ± standard.
RV, right ventricle; LV, left ventricle.

Four patients (15%) had angiographic signs of CAV 12 months after HTx with a median maximal stenosis of 33.4 ± 7.7%. We observed no differences in RV myocardial perfusion reserve at 12 months follow-up between patients with and without angiographic CAV ($P = 0.39$).

Correlation between right ventricular perfusion and right ventricular function

Table 3 shows the correlation between RV myocardial perfusion, RV function, and haemodynamic. As demonstrated, RV

Table 3 Correlation between RV myocardial perfusion and RV function, biomarkers, and haemodynamic parameters

	β1-coefficient (95% CI)	R value	P-value
Correlations to resting RV myocardial blood flow			
Log NT-ProBNP	3.9 (2.5;5.3)	0.61	<0.0001*
Log Troponin T	4.1 (2.3;6.0)	0.53	<0.0001
RV-FW-LS	-1.9 (-8.0;4.2)	-0.09	0.54
3D RV-EF	-5.9 (-15.3;3.4)	-0.18	0.21
TAPSE	-0.1 (-0.6;0.3)	-0.08	0.55
Cardiac index	-0.2 (-0.8;0.5)	-0.07	0.64
RV SW	-1.39 (-7.7;5.0)	-0.06	0.66
mRAP	3.5 (-0.4;7.4)	0.25	0.08
mPAP	5.1 (-2.3;12.4)	0.19	0.17
mPAWP	5.5 (0.8;10.2)	0.31	<0.05
Correlations to RV myocardial perfusion reserve			
Log NT-ProBNP	-0.6 (-0.8;-0.4)	-0.65	<0.0001*
Log Troponin T	-0.7 (-0.9;-0.4)	-0.62	<0.0001*
RV-FW-LS	0.9 (0.1;1.8)	0.30	<0.05
3D RV-EF	1.2 (-0.2;2.5)	0.24	0.08
TAPSE	0.04 (-0.02;1.0)	0.17	0.23
Cardiac index	0.1 (0.03;0.2)	0.37	<0.01
RV SW	0.7 (-0.2;1.5)	0.21	0.13
mRAP	-0.9 (-1.4;-0.3)	-0.43	<0.01*
mPAP	-1.1 (-2.1;-0.1)	-0.29	<0.05
mPAWP	-0.8 (-1.5;-0.2)	-0.34	<0.05

* $P < 0.05$ after adjustment for time since HTx.

RV, right ventricle; NT-ProBNP, N-terminal pro-brain natriuretic peptide; RV-FW-LS, right ventricular free wall longitudinal strain; RV-EF, right ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion; SW, stroke work; mRAP, mean right atrial pressure; mPAP, mean pulmonary arterial pressure; mPAWP, mean pulmonary artery wedge pressure.

perfusion at rest and RV perfusion reserve significantly correlated with NT-ProBNP and Troponin T levels. Furthermore, significant inverse correlations were observed between RV perfusion reserve and right and left heart filling pressure and a positive correlation with cardiac index. Interestingly, we observed a significant relation between RV myocardial flow reserve 12 months after HTx and maximal oxygen consumption ($r = 0.75$, $P < 0.01$) and peak exercise cardiac index ($r = 0.60$, $P < 0.05$).

The logarithmic value of NT-ProBNP significantly correlated with RV function in HTx patients (TAPSE: $r = -0.30$, $P < 0.0001$; 3D RV-EF: $r = -0.31$, $P < 0.0001$; RV-FW-LS: $r = -0.34$, $P < 0.0001$). Similarly, the logarithmic value of Troponin T significantly correlated with RV function in HTx patients (TAPSE: $r = -0.37$, $P < 0.0001$; 3D RV-EF: $r = -0.30$, $P < 0.0001$; RV-FW-LS: $r = -0.41$, $P < 0.0001$).

Discussion

In this comprehensive study of RV function during the first year after HTx by invasive haemodynamic, advanced echocardiography, and myocardial perfusion imaging, several important findings were revealed: (i) left and right heart filling pressures were normalized between 3 and 6 months after HTx; (ii) RV function by TAPSE, 3D RV-EF, and RV-FW-LS improved during follow-up, but remained reduced compared with healthy controls; (iii) RV perfusion reserve improved during the first year after HTx due to a gradual reduction in resting myocardial blood flow. Myocardial perfusion reserve was significantly associated with oxygen consumption and cardiac index at peak exercise; (iv) NT-ProBNP and Troponin T improved during follow-up but remained elevated compared with healthy controls. Both parameters were significantly associated with RV perfusion reserve and rejection episodes during follow-up.

During the first year after HTx, the RV adapts to the new loading and metabolic conditions. The RV function

increases but remains reduced compared with healthy controls measured by TAPSE and tissue Doppler 2D echocardiography.^{8,12,13} However, conventional measures of longitudinal RV function, such as TAPSE and tissue Doppler RV-S', are generally reduced after open-heart surgery and may not be representative of the overall RV performance.^{11,14,15} The present study supported previous findings of impaired RV function after HTx. Even though RV function was loading dependent, the function remained reduced after normalization of filling pressures. Importantly, the magnitude of RV dysfunction differed significantly between parameters. Thus, TAPSE was 44% lower but 3D RV-EF only 13% in HTx patients than healthy controls 12 months after HTx. Invasive RHC revealed normal RV stroke work, which indicates that the RV performance was not severely reduced in our HTx cohort at 12 months follow-up. This is supported by the poor relation between exercise capacity and RV function. We have previously evaluated RV function in long-term HTx patients⁹ demonstrating that RV function is significantly associated with CAV and cumulative rejections burden. However, only a subset of our patients had CAV at 12 months after HTx and no patients had severe angiographic CAV.

In our study, we noted a gradual improvement in RV perfusion reserve during follow-up. Several factors may influence early RV perfusion including oedema, endothelial dysfunction due to ischaemic transport damage, increased filling pressures, pericardial effusion, reduced RV function, and the catabolic status after major surgery. The significant association between RV perfusion and right heart filling pressures indicates that loading optimization is of utmost importance especially in the early phase after HTx. It is well known that LV perfusion reserve hold great prognostic value in HTx patients. Similarly, RV perfusion reserve seems of clinical importance as we noted a significant relation to peak exercise cardiac index and oxygen consumption. Recently, Fearon *et al.*¹⁶ conducted a randomized controlled trial in which HTx patients were randomized to ramipril versus placebo. In that study, invasively assessed coronary flow reserve increased by 52% in the ramipril group but only 23.5% in the placebo group. Ramipril did not affect the macrovascular CAV development. As RV perfusion reserve was strongly associated with LV perfusion reserve in our study, it seems likely that ramipril could also improve RV perfusion reserve and potentially influence exercise capacity in HTx patients.

The utility of Troponin T and NT-ProBNP for graft monitoring after HTx is increasingly recognized. Both parameters possess prognostic value and are associated with rejection episodes and CAV.^{17,18} However, the natural course during the first year after HTx has, until now, not been described. Interestingly, both parameters remain significantly elevated several months after HTx. Thus, this cannot solely be explained by the surgical trauma, mild impairment of renal

function or filling pressures. Interestingly, patients with biopsy proven rejection episodes had higher average levels of Troponin T and NT-ProBNP than patients without biopsy proven rejection. This is important as it indicates that myocardial inflammation and damage may be underlying causes of increased levels of Troponin T and NT-ProBNP during the first year after HTx. This was supported by the significant correlations between Troponin T and NT-ProBNP and RV functional parameters. Even though the role of Troponin T and NT-ProBNP for rejection monitoring has not been fully elucidated, rejection should be suspected if Troponin T and NT-ProBNP abruptly increases during the first year after HTx.

Limitations

The present study reflects a single centre experience with a relatively small number of patients. However, the prospective design with repeated measurements significantly improves the statistical power. The safety of adenosine is debatable^{19,20} and not all HTx patients tolerated adenosine challenge, especially early after HTx. Thus, we were unable to perform ¹⁵O-H₂O in all subjects. Finally, the software used for RV strain analysis is designed for LV strain analysis and the event timing was based on aortic valve opening and closing.

Conclusions

Normalization of left and right heart filling pressures are seen within the first 3 to 6 months after HTx. RV function improves during the first year after HTx, although it remains reduced compared with healthy controls. A stepwise improvement in RV perfusion reserve was demonstrated during the first year after HTx. RV perfusion reserve significantly correlated to right heart filling-pressure and peak exercise cardiac index.

Conflict of interest

None of the authors have conflicts of interest relevant to the present study.

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