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European Journal of Cardio-thoracic Surgery 37 (2010) 61–67

EUROPEAN JOURNAL OF
CARDIO-THORACIC
SURGERYwww.elsevier.com/locate/ejcts

Pretransplant pulmonary hypertension and long-term allograft right ventricular function[☆]

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Received 17 November 2008; received in revised form 14 May 2009; accepted 19 May 2009; Available online 20 October 2009

Abstract

Background: Graft right ventricular (RV) function is compromised directly posttransplant, especially in heart transplantation (HTx) recipients with pretransplant pulmonary hypertension (PH). Graft RV size and systolic function, and the effect of the recipient's pulmonary haemodynamics on the graft extracellular matrix are not well characterised in the patients long-term after HTx. **Aim:** Comparison of RV size and systolic function in HTx recipients' long-term posttransplant stratified by the presence of pretransplant PH. **Methods:** HTx survivors ≥ 2 years posttransplant were divided into group I without pretransplant PH (pulmonary vascular resistance, PVR < 2.5 Wood units, $n = 37$) and group II with PH (PVR ≥ 2.5 Wood units, $n = 16$). RV size and systolic function were measured using cardiac magnetic resonance imaging (CMR). The collagen content was assessed in septal endomyocardial biopsies obtained at HTx and at study inclusion. **Results:** Mean posttransplant follow-up was 5.2 ± 2.9 years (group I) and 4.9 ± 2.2 years (group II) ($p = 0.70$). PVR was 1.5 ± 0.6 vs 4.1 ± 1.7 Wood units pretransplant ($p < 0.001$), and 1.2 ± 0.5 vs 1.3 ± 0.5 Wood units at study inclusion ($p = 0.43$). Allograft RV size and systolic function were similar in both groups (p always ≥ 0.07). Collagen content at transplantation and at follow-up were not different (p always ≥ 0.60). **Conclusion:** Posttransplant normalisation of pretransplant PH is associated with normal graft RV function long-term after HTx.

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Keywords: Cardiac transplantation; Pretransplant pulmonary hypertension; Right ventricular function; Cardiac magnetic resonance imaging

1. Introduction

Heart transplantation (HTx) remains the most effective therapy for well-selected patients with severe congestive heart failure (CHF). With optimal medical treatment, CHF symptoms often may not worsen before the development of pulmonary hypertension (PH) [1,2]. This may explain the increasing numbers of HTx candidates with PH [3].

In the early postoperative phase, the allograft right ventricle (RV) often has difficulties to adapt to the pulmonary

circulation of the recipient. Especially in candidates with more severe PH, the risk for acute RV failure and early postoperative death is increased [4–9]. However, postoperative mortality is not increased in HTx recipients with mild-to-moderate pretransplant PH [5,9–12] warranting the acceptance of these patients as HTx candidates [3]. Nevertheless, more episodes of acute RV failure occur within the first 30 postoperative days in these patients [1,10]. In addition, dilatation and decreased systolic function of the graft RV are observed after the first postoperative year [13–15].

Pulmonary artery pressures normalise within the first 2 years after HTx in most recipients with pretransplant PH [10,12,16,21]. Because of the well-known interdependency of RV size and function and pulmonary artery pressure, we hypothesised that normalisation of graft RV size and function may occur after this time interval. This hypothesis was tested by recruiting HTx recipients who were more than 2 years posttransplant. In fact, pulmonary haemodynamics was similar in these study participants irrespective of the presence or absence of pretransplant PH. This permitted measurements of graft RV size and systolic function on a similar haemodynamic background.

Abbreviations: CMR, cardiac magnetic resonance; CHF, congestive heart failure; HTx, heart transplantation; LV, left ventricle; PA, pulmonary artery pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RV, right ventricle.

[☆] We thank the Inselspital Foundation and the Katharina Huber-Steiner Stiftung for financial support of this study. Financial support was provided by the Inselspital Foundation and the Katharina Huber-Steiner Foundation, Bern, Switzerland.

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2. Methods and materials

2.1. Study design

2.1.1. Inclusion and exclusion

This study was approved by the local Ethics Committee (study number 120/2002).

The inclusion protocol demanded a posttransplant time interval ≥ 2 years, right heart catheterisation before HTx, at 1 year and 2 years posttransplant, and at study inclusion, as well as the absence of \geq moderate tricuspid regurgitation. Sixty-six HTx recipients were screened after informed consent. Thirteen patients were not included because of claustrophobia ($n = 11$), or implanted pacemakers ($n = 2$). To test for the introduction of a selection bias due to the exclusion of patients < 2 years posttransplant, we analysed the survival of all HTx recipients ($n = 85$) transplanted at our centre during the same period of time.

2.1.2. Pretransplant treatment

In HTx candidates without PH, 24 patients had developed end-stage heart failure on the basis of ischaemic heart disease. Of these, 18 patients had been treated with bypass surgery, six cases received mitral valve reconstruction in addition. In HTx candidates with PH, six patients had developed end-stage heart failure on the basis of ischaemic heart disease. Four of these patients were treated with bypass surgery, in two cases in combination with mitral valve reconstruction. At transplantation, two patients in group 1 were on left ventricular assist device support, while one patient had been implanted in group 2.

At the time of HTx, all recipients were on optimal heart failure treatment. Diuretic treatment was adapted individually, based on the patient's documentation of body weight and regular control of the hepato-jugular reflux.

2.1.3. Postoperative treatment

All HTx recipients received in the intra- and immediate postoperative phase continuous NO inhalation. NO was titrated to achieve a low pulmonary artery pressure and was usually weaned over several hours before extubation. If tapering of NO was associated with an increase in pulmonary artery pressure, iloprost inhalations were started and titrated to maintain low pulmonary artery pressures. In general, treatment aimed at a balanced fluid management.

Study patients received immunosuppressive medication (cyclosporine, tacrolimus, azathioprine, mycophenolate acid, sirolimus, and prednisone) guided by side effects and regular histological monitoring of RV endomyocardial biopsies (postoperative weeks 1–4: every week; months 2–6: every 2–4 weeks; months 7–12: every 4–6 weeks; 2nd year: every 2–3 months; 3rd year: every 4 months; 4th/5th year: every 6 months; thereafter: once annually). In general, immunosuppression was started with a combination of cyclosporine, azathioprine and prednisone. Episodes of rejection resulted in modification of immunosuppressive therapy. Severe, haemodynamically relevant allograft rejection was not observed.

Antihypertensive treatment always targeted a blood pressure of $\leq 140/90$ mmHg at rest.

2.1.4. Study group definition

Participants were stratified by the presence of pretransplant PH into group I without PH (PVR < 2.5 Wood units) and group II with PH (PVR ≥ 2.5 Wood units) [5,10,11,16].

2.1.5. Measurements

2.1.5.1. Transthoracic echocardiographic measurements of graft RV function. Posttransplant echocardiograms were performed on a regular basis (postoperative weeks 1–4: every week; months 2–6: every other week; months 7–12: every 4 weeks; 2nd year: every 2–3 months; 3rd year: every 4 months; 4th/5th year: every 6 months; thereafter: once annually), or as clinically indicated. Acute RV graft dysfunction was diagnosed when the biplane RV to LV end-diastolic area ratio was > 0.6 [17]. All postoperative echocardiograms were included in the analysis. All episodes of acute RV dysfunction ($n = 9$) occurred within the first two postoperative years, and resolved with diuretic treatment ($n = 9$), and additional inhalation of iloprost in four cases.

2.1.5.2. Cardiac catheterisation. Haemodynamic data were obtained from pretransplant catheterisation (range: 16–194 days before transplantation), and annual routine catheterisations thereafter. Pretransplant reversibility was tested when PVR was ≥ 3 Wood units. Reversibility testing started with oxygen inhalation and was continued with nitric oxide inhalation (up to 80 parts per million, $n = 2$) or prostacyclin infusion (up to 10 ng/kg min, $n = 1$) when PVR remained ≥ 3 Wood units with oxygen. Cardiac output was determined by oxymetry (Fick principle).

2.1.5.3. Collagen content. The collagen content in septal biopsies is representative for ventricular fibrosis in the human heart [18]. Collagen constitutes by far the largest part of the extracellular matrix, and, its quantity was assessed as a surrogate for the extracellular matrix, similar to other reports [18,19]. In this study, routine septal biopsies of study participants obtained at transplantation and during follow-up were analysed. Sections of septal biopsies were stained with Masson's Trichrome [19], and the collagen content was measured by quantitative morphometry with an automated image analysis system (Leitz DMRB microscope using an objective PL Fluotar 20 \times lens coupled to a Pixelink PL-A662 high-resolution colour camera interfacing with Image-Pro Plus 5.1 software). Measurements were performed by an investigator blinded to clinical data.

2.1.5.4. CMR examination. Patients were examined supine using a 1.5 T whole body clinical MR system (Magnetom Sonata, Siemens Medical Solutions, Erlangen, Germany), with a six-channel phased array cardiac coil placed around their chest. Cardiac synchronisation was obtained from three electrodes placed on the left anterior hemithorax. The cardiac short axis was determined using three scout images: a mid-ventricular axial view, a cine breath-hold vertical long axis, and a cine breath-hold horizontal long axis. The basal short axis slice was positioned beyond the level of the mitral valve plane and the ventricles were imaged from the base towards the apex during short end expiratory breath-holds using contiguous short axis slices in 8 mm increments. Complete coverage of the ventricles with the short axis

acquisitions was confirmed on long-axis views. A cine steady state free precession technique (TR/TE/flip 24/1.5/65; slice thickness 8 mm; temporal resolution 25 ms) was used.

2.1.5.5. CMR image analysis. All analyses were done off-line in random order by experienced observers blinded to clinical data. Image analysis was carried out on a dedicated workstation using commercially available software (Argus version VA50C, 2002, Siemens Medical Solutions, Erlangen, Germany). In each cine short axis view, the end-diastolic image was chosen at the beginning of the QRS complex as the phase with the largest intraventricular area. End-systolic images were chosen as the phase with the smallest intraventricular area. End-diastolic and end-systolic endomyocardial borders were manually traced for each slice. From the area within the contours and the slice thickness

(8 mm), the evaluation program automatically determined RV end-diastolic volume (RVEDV) and RV end-systolic volume (RVESV), according to modified Simpson's rule (disk summation, no geometrical assumption). The difference between RVEDV and RVESV represents the stroke volume (SV). RV ejection fraction (RVEF) was calculated as $(RVEDV - RVESV) / RVEDV \times 100$. Tables 3 and 4 provide measurements indexed to body surface area.

2.1.6. Clinical data

Clinical and donor specific data were obtained from chart review.

2.1.7. Statistical analysis

Measurements and clinical parameters are expressed as mean values ± 1 standard deviation (SD), or numbers and

Table 1
Demographic and clinical characteristics of study groups.

	All patients	PVR <2.5 Wood units	PVR \geq 2.5 Wood units	<i>p</i>
Number (%)	53	37 (70)	16 (30)	
Demographics				
Time on waiting list (months)	5.9 \pm 6	6.4 \pm 6.9	5 \pm 4	0.43
Age at HTx (years)	51 \pm 13	50 \pm 13	53 \pm 12	0.45
Donor age (years)	37 \pm 14	37 \pm 14	37 \pm 15	0.95
Time posttransplant (years) (mean) (range in years)	5.1 \pm 2.7 (2.0–8.9)	5.2 \pm 2.9 (2.1–8.9)	4.9 \pm 2.2 (2.0–8.1)	0.70
Etiology of CHF				
Ischaemic cardiomyopathy (%)	57	66	36	0.28
Measurements at HTx				
Recipient body weight (kg)	75 \pm 12	76 \pm 11	72 \pm 14	0.36
Donor body weight (kg)	74 \pm 11	75 \pm 10	71 \pm 11	0.19
Recipient/donor body mass index	1.0 \pm 0.3	1.1 \pm 0.2	1.0 \pm 0.3	0.61
Risk factors				
Diabetes (%)	26	19	43	0.09
Body mass index (BMI)	25 \pm 4	26 \pm 4	24 \pm 3	0.21
Dyslipidemia (%)	15	15	14	0.97
Number of \geq moderate rejection episodes	1.76 \pm 2.01	1.57 \pm 1.82	2.19 \pm 2.37	0.31
Mean allograft rejection score (ISHLT)	1.3 \pm 1.4	1.4 \pm 1.4	1.3 \pm 1.3	0.86
Immunosuppressive medication				
Cyclosporine				
Days on cyclosporine	1710	1674	1791	0.65
Total dose of cyclosporine (g)	331493	328993	336694	0.87
Tacrolimus				
Days on tacrolimus	744	688	838	0.71
Total dose of tacrolimus (g)	5087	3828	7185	0.27
Azathioprine				
Days on azathioprine	883	809	1026	0.43
Total dose of azathioprine (g)	59640	52363	73708	0.27
Mycophenolate				
Days on mycophenolate	972	911	1,011	0.37
Total dose of mycophenolate (g)	2421013	2295487	2683,477	0.51
Sirolimus				
Days on sirolimus	634	794	236	0.36
Total dose of sirolimus (mg)	2287	2722	1200	0.65
Prednisone				
Days on prednisone	1605	1588	1643	0.79
Total dose of prednisone (mg)	13713	13970	13153	0.67
Other medication				
Diuretics (%)	79	70	100	0.42
β -Blocker (%)	38	27	60	0.51
Calcium antagonist (%)	94	92	100	0.50
ACE-I/ARB (%)	64	64	64	0.98

Table 2
Haemodynamic parameters pre- and posttransplant.

	All patients	PVR <2.5 Wood units	PVR ≥2.5 Wood units	<i>p</i>
Number (%)	53	37 (70)	16 (30)	
Pretransplant				
Interval of PVR measurement to HTx, days HTxHTx	95 ± 75	93 ± 82	101 ± 64	0.73
Mean PA (mmHg)	30 ± 13	24 ± 10	43 ± 9	<0.001
Mean PCW (mmHg)	21 ± 10	18 ± 10	30 ± 6	<0.001
Mean transpulmonary gradient (mmHg)	8.5 ± 4.4	6.5 ± 2.8	12.8 ± 4.3	<0.001
Mean PVR (Wood units)	2.3 ± 1.6	1.5 ± 0.6	4.1 ± 1.7	<0.001
1-year posttransplant				
RVEDP (mmHg)	4.4 ± 2.9	4.1 ± 2.9	5.1 ± 3.1	0.31
PA systolic (mmHg)	24.1 ± 8.3	22.6 ± 7.8	28.9 ± 7.9	0.04
Mean PA (mmHg)	16 ± 5	15 ± 5	18 ± 6	0.09
Mean PCW (mmHg)	9 ± 5	9 ± 4	10 ± 6	0.34
Mean transpulmonary gradient (mmHg)	6.9 ± 2.9	6.5 ± 2.9	7.7 ± 2.8	0.17
Mean PVR (Wood units)	1.2 ± 0.5	1.2 ± 0.5	1.3 ± 0.5	0.27
Posttransplant at CMR				
RVEDP (mmHg)	4.4 ± 3.0	4.6 ± 2.7	4.1 ± 3.7	0.61
PA sys (mmHg)	23.4 ± 7.3	23.4 ± 7.7	24.2 ± 6.3	0.69
Mean PA (mmHg)	16 ± 5	16 ± 5	15 ± 5	0.85
Mean PCW (mmHg)	8 ± 4	8 ± 4	7 ± 4	0.60
Mean transpulmonary gradient (mmHg)	7.6 ± 3.0	7.6 ± 2.9	7.7 ± 3.3	0.90
Mean PVR (Wood units)	1.2 ± 0.5	1.2 ± 0.5	1.3 ± 0.5	0.43
Episodes of acute RV dysfunction (% patients)	17	11	31	0.07

percentages, as appropriate. Normally distributed continuous variables were compared by a one-way analysis of variance (ANOVA). For non-normally distributed variables comparison was done using Mann–Whitney-*U* testing. For comparison of categorical variables chi-square testing or Fisher's exact test was performed, as appropriate. The cumulative survival rates were estimated using the Kaplan–Meier method, differences in survival curves were compared with the two-sided log-rank test. Differences were considered significant at a *p*-value of <0.05.

3. Results

3.1. Clinical characteristics

Pretransplant demographics, risk factors, as well as measurements at HTx, or medication posttransplant were not different between the study groups (Table 1).

3.2. Survival analysis of the HTx cohort transplanted in the same time interval at the local centre

Overall survival of orthotopic HTx recipients transplanted in the same time interval (*n* = 85) at the local centre as the study patients was 84% after the first year, 79% after 5 years, and 72% after 10 years. Log-rank analysis revealed no significant difference when comparing the survival of HTx recipients with or without pretransplant PH (*n* = 24 vs *n* = 61 patients, *p* = 0.073). In detail, 30 day survival: 75% vs 92%; 1 year survival: 73 vs 88%; 5 years survival: 68 vs 84%; 10 years survival: 60 vs 76%. In addition, RV graft failure related mortality was not different at 30 days and 1 year posttransplant (*p* always ≥0.38).

3.3. Haemodynamic characteristics of study patients with pretransplant PH

Of the 16 patients included, eight presented with mild PH (PVR ≥2.5 and <3.5 Wood units), five with moderate PH (PVR ≥3.5 and <5 Wood units), and 3 with severe PH (PVR ≥5 Wood units) of recent onset. Pretransplant, mean pulmonary artery pressure (PA), transpulmonary gradient (TPG) and pulmonary wedge pressure (PCW) were higher (*p* always <0.001) in HTx recipients with PH. One year posttransplant, only systolic PA remained elevated (28.9 ± 7.9 vs 22.6 ± 7.8 mmHg, *p* = 0.04) in these patients. At study inclusion, pulmonary haemodynamics were no longer different between groups (Table 2).

3.4. Echocardiographic measurements of graft end-diastolic LV/RV ratio

The incidence of episodes with acute RV dysfunction was by trend higher in HTx recipients with pretransplant PH (31% vs 11% of study patients, *p* = 0.07). (Table 2)

3.5. RV CMR characteristics

Indexed end-diastolic and end-systolic RV volumes, and RV ejection fraction were not different between groups. In group II patients, heart rate was lower (77 ± 9 vs 86 ± 13 bpm; *p* = 0.032) as well as cardiac output (6.9 ± 1.5 vs 5.6 ± 1.3; *p* = 0.01) (Table 3).

In addition, the dependency of RV size and systolic function on the time interval posttransplant was explored. The study groups were subdivided by the median time interval posttransplant (5 years). In HTx recipients with pretransplant PH, indexed graft RV stroke volume was lower in the time interval 2–5 years after surgery (38 ± 9 vs

Table 3
CMR LV and RV measurements.

	All patients	PVR <2.5 Wood units	PVR ≥2.5 Wood units	p
Number (%)	53	37 (70)	16 (30)	
CMR LV parameters				
LVEDVI (ml/m ²)	66 ± 16	68 ± 15	63 ± 17	0.30
LVESVI (ml/m ²)	25 ± 8	25 ± 7	25 ± 9	0.78
LVSVI (ml/m ²)	41 ± 11	44 ± 11	38 ± 10	0.07
LV ejection fraction (%)	63 ± 7	64 ± 6	60 ± 8	0.19
Heart rate (beats per min)	83 ± 13	86 ± 13	77 ± 9	0.03
LV cardiac output (l/min)	6.5 ± 1.6	6.9 ± 1.5	5.6 ± 1.3	0.01
CMR RV parameters				
RVEDVI (ml/m ²)	71 ± 17	73 ± 18	67 ± 16	0.23
RVESVI (ml/m ²)	28 ± 9	28 ± 9	29 ± 9	0.80
RVSVI (ml/m ²)	43 ± 11	45 ± 11	38 ± 9	0.07
RV ejection fraction (%)	61 ± 8	61 ± 8	59 ± 8	0.47
RV cardiac output (l/min)	6.7 ± 1.7	7.1 ± 1.7	5.6 ± 1.3	0.01

Table 4
CMR LV and RV measurements in patients 2–5 and >5 years posttransplant.

	PVR <2.5 Wood units	PVR ≥2.5 Wood units	p	PVR <2.5 Wood units	PVR ≥2.5 Wood units	p
Time interval post-HTx (years)	2–≤5	2–≤5		>5	>5	
Number	26	9		11	7	
CMR LV parameters						
LVEDVI (ml/m ²)	71 ± 15	65 ± 18	0.46	68 ± 13	67 ± 17	0.91
LVESVI (ml/m ²)	25 ± 6	28 ± 11	0.53	26 ± 7	23 ± 8	0.56
LVSVI (ml/m ²)	45 ± 12	36 ± 9	0.05	42 ± 8	43 ± 11	0.79
LV ejection fraction (%)	35 ± 6	32 ± 6	0.2	33 ± 5	34 ± 4	0.75
Heart rate (beats per min)	86 ± 14	74 ± 9	0.01	87 ± 11	81 ± 8	0.32
LV cardiac output (l/min)	7 ± 1.5	4.9 ± 0.9	0.003	6.8 ± 1.4	6.6 ± 1.1	0.92
CMR RV parameters						
RVEDVI (ml/m ²)	76 ± 22	68 ± 17	0.33	77 ± 17	65 ± 16	0.21
RVESVI (ml/m ²)	29 ± 13	31 ± 10	0.79	32 ± 8	23 ± 7	0.05
RVSVI (ml/m ²)	47 ± 13	38 ± 9	0.04	45 ± 11	42 ± 11	0.66
RV ejection fraction (%)	34 ± 7	30 ± 6	0.18	31 ± 4	34 ± 4	0.26
RV cardiac output (l/min)	7.3 ± 1.8	5 ± 1	0.001	7.3 ± 1.7	6.4 ± 1.2	0.32

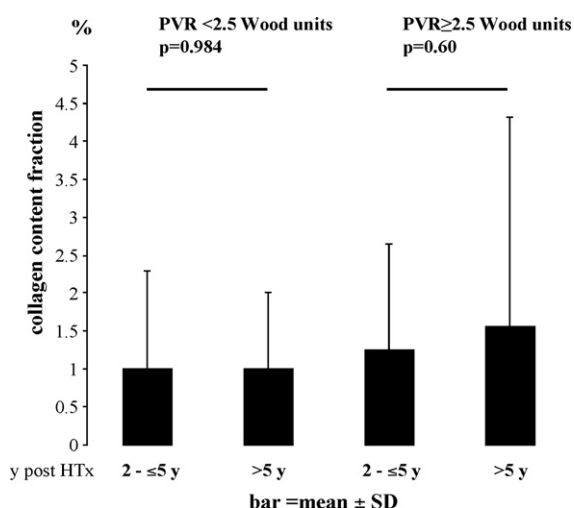


Fig. 1. Collagen content in graft RV endomyocardial biopsies. Bar graphs represent the collagen content ±1 standard deviation in HTx recipients with pretransplant PVR <2.5 Wood units and PVR ≥2.5 Wood units, 2–5 years or ≥5 years (y) post-HTx, respectively

47 ± 13 ml/m², $p = 0.048$). No difference remained between groups more than 5 years after transplantation (45 ± 11 vs 42 ± 11 ml/m²; $p = 0.66$) (Table 4).

3.6. Collagen content of endomyocardial biopsies

Collagen content was not different in RV biopsies obtained pre-implantation and at study inclusion. Likewise, no differences were observed when the study groups were subdivided by the median of the posttransplant interval (Fig. 1).

4. Discussion

The major finding of this study is that allograft RV size and systolic function long-term posttransplant is similar in HTx recipients with normalised pretransplant PH and in HTx recipients with normal pulmonary artery pressure pretransplant. This finding is important in the context of the increasing numbers of HTx candidates with pulmonary hypertension.

4.1. Study design

The hypothesis that allograft RV size and systolic function may normalise late after HTx in recipients with pretransplant PH was tested using a cross-sectional study design in a local HTx cohort. Several reports indicate that normalisation of pretransplant PH occurs within the first two postoperative years [10,12]. Therefore, this study included HTx recipients who were ≥ 2 years after transplantation. In accordance with the literature, pretransplant PH had resolved incompletely in our study patients 1 year posttransplant. At study inclusion, however, pulmonary haemodynamics were no longer different between HTx recipients with or without pretransplant PH. While this reflects the adequacy of the inclusion criterion in this regard, studying HTx recipients who survived the first 2 years posttransplant might select patients with a better outcome per se, which might limit the significance of this study. Survival was not different in a Kaplan–Meier survival analysis which included all HTx recipients grafted in the same period of time at our centre whether presenting with or without pulmonary hypertension. On this basis we can exclude the introduction of relevant a selection bias.

4.2. Pulmonary haemodynamics and graft RV function

Acute dysfunction of the graft RV is one of the major concerns in the early postoperative course after HTx. Usually, acute graft RV failure is reported on the basis of clinical diagnosis [8–10]. This study records RV dysfunction based on echocardiographic diagnosis, which may explain the higher incidence of episodes with acute RV dysfunction reported here [10]. Clinically, most cases of acute RV dysfunction in our study participants resolved with intensified diuretic treatment suggesting that adequate fluid management supports the adaptation of the graft RV to the recipient's pulmonary circulation.

Graft RV size and systolic function were assessed by CMR which is most accurate for RV assessments [22]. Long-term after HTx, graft RV size and systolic function was not different whether PH had been present or absent pretransplant. This observation corresponds with previous imaging studies, which had studied allograft RV size and volumes in HTx recipients long-term posttransplant [20,23], but had not stratified for pretransplant PH. In this study population, RV systolic function did not recover in parallel with the normalisation of pulmonary artery pressures, as RV stroke volumes were lower in HTx recipients with pretransplant PH who were 2–5 years after HTx when compared to those with an interval of more than 5 years posttransplant. Several factors may be relevant for this transitory decreased systolic function in these patients; however, the collagen content should not play a relevant role as it was not different when measured in biopsies taken at HTx and in HTx recipients with pretransplant PH who were 2–5 years after HTx.

4.3. Limitations

Limitations of this study are the smaller number of patients included and its cross-sectional design; however, to our knowledge, this is the largest CMR study on graft RV function. Furthermore, this study lacks serial measurements

of graft RV size and function, which may provide additional information; [15] however, the principal finding of this study remains.

Contributors

A. Wahl: performed and analysed CMR studies, wrote the manuscript; M. Feller: performed collagen content studies and collection of clinical data; E. Wigger: performed CMR studies and collection of clinical data; H. Tanner: performed statistical analysis; C. Stoupis: performed CMR studies; T. Carrel: analysed clinical data; P. Mohacsi: analysed clinical data; R. Hullin: designed the study, analysed the data, wrote the manuscript.

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