Right ventricular recovery after bilateral lung transplantation for pulmonary arterial hypertension

Gorter, Thomas M.; Verschuuren, Erik A. M.; van Veldhuisen, Dirk J.; Hoendermis, Elke S.; Erasmus, Michiel E.; Bogaard, Harm J.; Noordegraaf, Anton Vonk; Berger, Rolf M. F.; van Melle, Joost P.; Willems, Tineke P.

Published in:
Interactive Cardiovascular and Thoracic Surgery

DOI:
10.1093/icvts/ivx025

Interactive CardioVascular and Thoracic Surgery 24 (2017) 890–897
doi:10.1093/icvts/ivx025 Advance Access publication 3 March 2017

ORIGINAL ARTICLE

Cite this article as: Gorter TM, Verschuuren EAM, van Veldhuisen DJ, Hoendermis ES, Erasmus ME, Bogaard HJ *et al.* Right ventricular recovery after bilateral lung transplantation for pulmonary arterial hypertension. Interact CardioVasc Thorac Surg 2017;24:890–7.

Right ventricular recovery after bilateral lung transplantation for pulmonary arterial hypertension†

Thomas M. Gorter[a,*], Erik A.M. Verschuuren[b], Dirk J. van Veldhuisen[a], Elke S. Hoendermis[a], Michiel E. Erasmus[c], Harm J. Bogaard[d], Anton Vonk Noordegraaf[d], Rolf M.F. Berger[e], Joost P. van Melle[a,‡] and Tineke P. Willems[f,‡]

[a] Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands
[b] Department of Pulmonary Diseases and Tuberculosis, University of Groningen, University Medical Center Groningen, Groningen, Netherlands
[c] Department of Thoracic Surgery, University of Groningen, University Medical Center Groningen, Groningen, Netherlands
[d] Department of Pulmonary Medicine, VU University Medical Center, Amsterdam, Netherlands
[e] Department of Paediatric Cardiology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands
[f] Department of Radiology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands

* Corresponding author. Department of Cardiology, University Medical Center Groningen, University of Groningen, Hanzeplein 1, PO Box 30.001, 9700 RB Groningen, Netherlands. Tel: +31-50-3615995; fax: +31-50-3611347; e-mail: tm.gorter@umcg.nl (T.M. Gorter).

Received 22 September 2016; received in revised form 9 December 2016; accepted 3 January 2017

Abstract

OBJECTIVES: Pulmonary arterial hypertension (PAH) is a progressive and often fatal disease characterized by increased pulmonary vascular resistance (PVR) and right ventricular (RV) failure. End-stage PAH is often an indication for a lung transplant (LTX). Our goal was to study ventricular recovery using cardiac magnetic resonance imaging late after LTX.

METHODS: We studied 10 patients with PAH who underwent isolated bilateral LTX. RV and left ventricular (LV) volumes, function and mass were measured. In addition, the RV stroke volume/end-systolic ratio (SV/ESV), the LV eccentricity index, the RV/LV volume ratio, the area of the tricuspid valve annulus and the severity of tricuspid regurgitation (TR) were calculated.

RESULTS: The median age was 44 [30–54] years and the mean PVR was 1020 ± 435 dynes·s·cm^{-5}. Six patients had ≥ moderate TR. After LTX, the RV ejection fraction increased from 32 to 64% ($P < 0.001$) and both RV volume (from 118 to 51 ml/m^2, $P < 0.001$) and RV mass (from 69 to 33 g/m^2, $P < 0.001$) decreased. The mean SV/ESV ratio increased from 0.5 to 1.9 ($P < 0.001$) and the LV mass increased from 55 to 61 g/m^2 ($P = 0.005$). There was a decrease in both the LV eccentricity index (from 2.8 to 1.1, $P < 0.001$) and the RV/LV volume ratio (from 2.3 to 0.8, $P < 0.001$). The area of the tricuspid valve annulus also decreased (from 9.8 to 4.6 cm^2/m^2, $P < 0.001$); no patient had ≥ mild TR post-LTX.

CONCLUSIONS: Cardiac magnetic resonance imaging confirms ventricular recovery after isolated bilateral LTX for end-stage PAH.

Keywords: Pulmonary arterial hypertension • Right ventricular failure • Lung transplantation • Cardiac magnetic resonance imaging

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive and often fatal disease characterized by increased pulmonary vascular resistance, which leads to right ventricular (RV) dysfunction and failure [1]. Although emerging treatment strategies have improved prognosis in these patients, the number of deaths remains unacceptably high [2].

Specific pharmacological therapies that target PAH aim to reduce pulmonary vascular resistance and improve RV cardiac output, yet they do not always succeed, and RV function may further deteriorate despite advanced treatment [3]. For patients with such an inadequate response to drug therapy, a lung transplant (LTX) may be indicated as a destination therapy [4]. However, the timing of LTX is still a matter of debate, and a significant number of patients die while they are on the waiting list [5]. Furthermore, the type of transplant procedure, i.e. LTX versus a heart-lung transplant (H-LTX), is still subject to debate. Survival rates were previously reported to be similar between bilateral LTX and H-LTX. However, patients with the most severe disease tend to receive H-LTX more often [6, 7]. Given the shortage of organs for transplant, it is important to elucidate whether it is safe to perform isolated LTX instead of H-LTX in patients with PAH and severe RV failure.

Previous studies that investigated the effects of LTX demonstrated improvement in pulmonary haemodynamics and RV systolic function [8–15]. However, these studies were either outdated or based primarily on echocardiographic results. Due to the known limitations for a reliable assessment of RV morphology and

† Presented at the ESC Heart Failure Congress, Florence, Italy, 21–24 May, 2016.

‡ These two authors contributed equally to this work.

function with echocardiographic examinations, cardiac magnetic resonance imaging (CMRI) is currently the preferred modality for this purpose. Furthermore, these studies were performed at a time when treatment options were limited, and patients often received transplants early in the development of the disease. During chronic PAH, the initial RV remodelling is adaptive to the increased afterload. Yet over time, RV remodelling becomes maladaptive and progressive RV failure develops [16]. Whether this advanced RV remodelling process is reversible after LTX remains unknown. Therefore, our goal was to study ventricular recovery after isolated bilateral LTX for long-standing PAH using CMRI.

MATERIALS AND METHODS

All patients referred to the University Medical Center Groningen (UMCG, Groningen, Netherlands) between 2000 and 2015 with (i) World Health Organization (WHO) Group 1 PAH [4] and (ii) who were considered eligible for bilateral LTX were screened. Patients were included if pre- and postoperative CMRI data were available. Exclusion criteria were simultaneous heart or liver transplant or insufficient image quality for the assessment of ventricular volume and function. Baseline demographics, primary diagnosis, clinical characteristics (i.e. World Health Organization functional class and 6-min walk distance) and type of PAH-targeted therapy were documented. In addition, preoperative right heart catheterization measurements and the N-terminal of the prohormone brain natriuretic peptide were collected. Disease duration was determined as the period between the first diagnostic right heart catheterization and the LTX.

Examinations and assessments used for the present study were performed according to standard protocols and within the context of regular care. All patients accepted for the LTX provided written informed consent for their data being used for research purposes. Ethical approval for the use of these data was obtained by the local ethical committee.

Surgical procedures at the UMCG were performed with a bilateral anterior thoracotomy. Both donor lungs were consecutively placed using bronchial, pulmonary artery and vein anastomoses.

Cardiac magnetic resonance imaging protocol

CMRI studies at the UMCG and VU University Medical Center (Amsterdam, Netherlands) were performed on a Siemens 1.5-T scanner (Erlangen, Germany) and studies at the Erasmus Medical Center (Rotterdam, Netherlands) were performed on a GE Healthcare 1.5-T scanner (Milwaukee, WI, USA). ECG-gated cine loop images with breath holding were obtained using retrospectively gated, steady-state, free-precession sequences. Long-axis slices were acquired in the 4-chamber view. Additional short-axis slices were acquired fully covering both ventricles.

Ventricular measurements were performed by contouring the short-axis endo- and epicardial boarders of both ventricles with semiautomatic, threshold-based segmentation using QMass 7.6 (Medis, Leiden, Netherlands), as previously described [17]. End-diastolic volume, end-systolic volume, stroke volume, ejection fraction (EF) and mass were calculated using summation of slices multiplied by slice thickness. Absolute measurements were indexed for body surface area using the simplified calculation of Mosteller and were compared with previously proposed cut-off values for the development of end-stage RV failure and death [18]. RV trabecular and papillary masses were quantified as mass within the endocardial border of the RV. RV wall mass was quantified as total mass minus trabecular mass. The trabecular ratio was calculated as trabecular mass divided by wall mass.

Right atrial volume indexed for body surface area (RAVi) and left atrial volume index were measured with CMRI on the apical 2-chamber view for RAVi and on the apical 2- and 4-chamber views for left atrial volume index using the area-length method [19].

RV-arterial coupling was estimated using the volume method (i.e. stroke volume/end-systolic volume), with a previously suggested optimal ratio between 1.5 and 2.0 [20]. Interventricular septal bowing towards the LV is an indication for increased RV afterload. The degree of septal bowing was assessed using the LV eccentricity index, which was obtained in end-systole by measuring the short-axis LV mid diameter parallel to the septum divided by the LV mid diameter perpendicular to the septum [21]. Under normal circumstances, the LV is O-shaped throughout the cardiac cycle and the LV eccentricity index remains approximately 1; however, it increases with a leftward septal shift. Subsequently, RV/LV volume and mass ratios were calculated.

The diameter of the tricuspid valve annulus was obtained on the long-axis view by measuring the distance between the lateral and septal tricuspid valve annuli in end-systole. Furthermore, the surface area of the tricuspid valve annulus was measured on the basal short-axis images by tracing the annular surface in end-systole.

Echocardiographic analysis

Echocardiographic images acquired on Vivid systems (GE, Horton, Norway) with a 2.5–3.5-mHz probe were analysed using GE EchoPAC version BT12. Tricuspid annular plane systolic excursion was obtained with M-mode parallel to the RV free wall and across the tricuspid annular plane. RV peak pressure was estimated by calculating the systolic trans-tricuspid gradient [22]. For determining the severity of tricuspid regurgitation (TR), colour flow Doppler, pulsed wave Doppler, continuous wave Doppler, the width of the vena contracta, peak tricuspid systolic inflow and hepatic flow were used. TR was subsequently graded into absent/trivial (Grade 0), mild (Grade 1), moderate (Grade 2) and severe (Grade 3) [22].

Statistical analysis

Data were presented as *n* (%), mean ± standard deviation or median (interquartile range [IQR]). Differences in continuous variables and categorical variables between groups were tested using the Mann–Whitney *U*-test and the Fisher exact test. Differences between continuous variables within groups were tested using paired samples *t*-tests. Correlations were performed using the Pearson *r*. Values with $P < 0.05$ were considered statistically significant. Statistical analyses were performed using SPSS (Version 22, 2013).

RESULTS

A total of 26 patients with World Health Organization Group 1 PAH underwent isolated bilateral LTX; 10 of these patients were included in the present study (Fig. 1). Eight patients died after LTX before postoperative CMR was performed and only 1 of these patients had undergone preoperative CMRI. None of these patients died of acute RV failure, as seen in Fig. 1. Baseline characteristics of included ($n = 10$) and excluded ($n = 16$) patients are

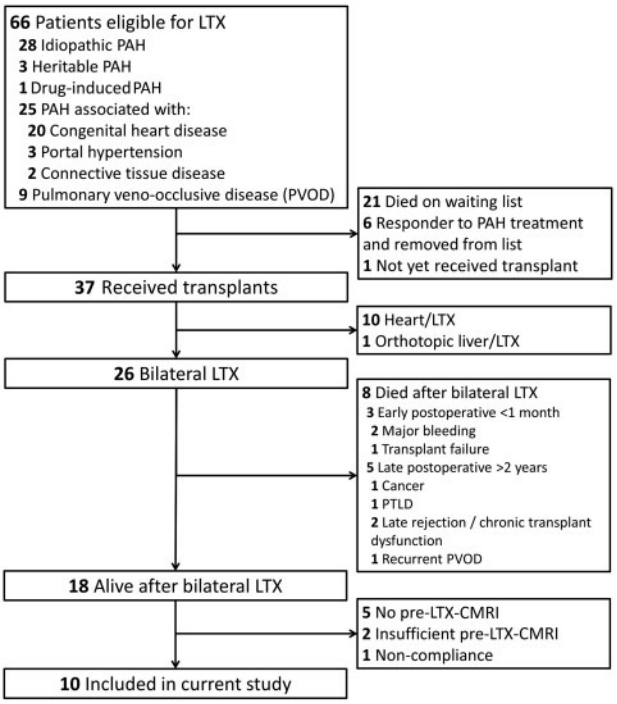

Figure 1: Flow of Group 1 pulmonary arterial hypertension patients listed for bilateral LTX. CMRI: cardiac magnetic resonance imaging; LTX: lung transplant; PAH: pulmonary arterial hypertension; PTLD: post-transplant lymphoproliferative disorder; PVOD pulmonary veno-occlusive disease.

shown in Table 1. The interval between right heart catheterization and LTX was 3.7 [1.7–4.9] years and the interval between preoperative echocardiographic assessment and LTX was 4.7 [1.9–13.5] months. There were no differences between the 2 groups. Baseline N-terminal of the prohormone brain natriuretic peptide was 1277 [IQR 707–2112] ng/l. After LTX, N-terminal of the prohormone brain natriuretic peptide decreased to a median value of 488 [274–834] ng/l, although it was not statistically significant ($P = 0.21$).

Surgical procedure

In 1 patient, an atrial septal defect was closed during the procedure. In 2 patients who had undergone previous atrial septostomy, the septum was also closed.

In 8 patients, the operation was performed with cardiopulmonary bypass. Of these, 3 patients were postoperatively transferred to the intensive care unit with venoarterial extracorporeal membrane oxygenation (VA-ECMO) due to pulmonary oedema. VA-ECMO was removed after 4, 6 and 7 days, respectively. In 1 patient, the operation was performed without cardiopulmonary bypass or postoperative VA-ECMO. In another patient, femoral VA-ECMO was placed with the patient under local anaesthesia before the general anaesthesia was introduced. In this patient, the operation was performed with the patient under VA-ECMO, which continued 1 day postoperatively. Details of the preoperative and early and late postoperative treatment per patient are presented in the Supplementary File.

Ventricular recovery after lung transplantation

The median interval between LTX and postoperative CMRI was 3.1 [1.4–4.8] years. A significant change was shown for all parameters, except for left ventricular end-diastolic volume index and LVEF (Table 2). RV trabecular mass decreased from 29 to 13 g/m^2 ($P < 0.001$) and the RV trabecular mass ratio from 0.42 to 0.38 ($P = 0.048$).

Improvement in RV volume and mass was robust in all patients (Fig. 2). None of the patients remained above the prognostic cut-off for right ventricular end-diastolic volume index (RVEDVi) and RV mass index or below the cut-off for RVEF after LTX, as illustrated by the horizontal dotted lines in Fig. 2A–C. The stroke volume/end-systolic volume ratio increased in all patients from 0.5 to 1.9, as seen in Fig. 2D. LTX resulted in normalization of RV/LV volume ($P < 0.001$) and mass ratio ($P < 0.001$) in all patients (Fig. 2E and F).

Change in LV measurements is demonstrated in Fig. 3. Three patients had an important reduction in LVEF after LTX. One patient had a mild myocardial infarction between LTX and postoperative CMRI. The second patient had renal failure and was listed for a renal transplant. The third patient had reduced LVEF and RVEF for which no apparent cause could be identified.

The median preoperative RAVi was 102 [IQR 37–195] ml/m^2 and the RAVi decreased after LTX to 43 [IQR 26-76] ml/m^2 ($P = 0.007$). The median left atrial volume index slightly increased from 20 [IQR 16–32] to 36 [IQR 25–50] ml/m^2, although it was not statistically significant ($P = 0.08$).

Figure 4 shows a patient with PAH and CMRI before and almost 10 months after LTX. In this patient, RVEF normalized from 25 to 60%, RVEDVi from 83 to 41 ml/m^2 and RV mass from 58 to 29 g/m^2.

The changes in RVEDVi, RVEF and RV mass after LTX were not correlated with the interval between LTX and the postoperative CMRI ($P = 0.66$, 0.27 and 0.37, respectively). In addition, changes in the left ventricular end-diastolic volume index, LVEF and LV mass index showed no correlation with the postoperative interval ($P = 0.13$, 0.83 and 0.93, respectively). There was no relationship between this interval and the change in LV eccentricity index ($P = 0.38$) nor in the change in RV/LV volume and mass ratio after LTX ($P = 0.84$ and 0.87, respectively).

Tricuspid valve regurgitation

At baseline, 4 patients had Grade 0 or 1 TR and 6 patients had Grade 2 or 3 (Table 1). Figure 5A shows that the area of the tricuspid valve annulus was significantly larger in patients with Grade 2 and 3 TR than in patients with Grade 0 and 1 TR ($P = 0.025$). The area of the tricuspid valve annulus correlated strongly with the RVEDVi ($r = 0.83$, $P = 0.003$).

LTX reduced the diameter and area of the tricuspid valve annulus, as illustrated in Fig. 5B and C. The median interval between the postoperative echocardiographic study and transplantation was 3.5 [IQR 1.3–4.7] years. After LTX, 1 patient had Grade 1 TR and no patient had Grade 2 and 3 TR. The reduction in the tricuspid area also correlated with the reduction in RVEDVi after LTX ($r = 0.70$, $P = 0.025$).

DISCUSSION

The results of the present study demonstrated marked improvements in RV function, morphology and arterial coupling after LTX. In all patients, normalization of biventricular morphology and function was observed. Finally, none of the patients

Table 1: Characteristics of patients who underwent LTX for PAH (*n* = 26)

Characteristics	Included patients (*n* = 10)	Excluded patients (*n* = 16)	*P*-value
Age, years	44.0 [30.1–53.5]	46.6 [29.5–53.4]	0.70
Men/women	3/7	7/9	0.68
Diagnosis			0.64
IPAH, *n* (%)	6 (60)	11 (69)	
HPAH, *n* (%)	1 (10)	0	
Drugs and toxins induced, *n* (%)	1 (10)	0	
PAH-CTD, *n* (%)	0	2 (13)	
PAH-CHD, *n* (%)	1 (10)	1 (6)	
PVOD, *n* (%)	1 (10)	2 (13)	
Disease duration, years	7.4 [6.5–10.1]	4.7 [2.0–9.4]	0.08
Time on waiting list, months	7.9 [2.2–12.5]	11.4 [6.8–23.1]	0.18
PAH therapy[a]			0.55
None, *n* (%)	0	1 (6)	
Mono, *n* (%)	0	3 (19)	
Dual, *n* (%)	6 (60)	8 (50)	
Triple, *n* (%)	4 (40)	4 (25)	
WHO-FC (*n* = 26)			0.68
III, *n* (%)	7 (70)	9 (56)	
IV, *n* (%)	3 (30)	7 (44)	
6-MWD, *m* (*n* = 26)	335 ± 154	361 ± 113	0.62
Right heart catheterization (*n* = 26)			
SPAP, mmHg	89 ± 26	81 ± 24	0.46
DPAP, mmHg	38 ± 12	34 ± 15	0.50
MPAP, mmHg	58 ± 17	53 ± 17	0.42
PCWP, mmHg	5	5	0.15
PVR, dynes·s·cm^{-5}	1020 ± 435	858 ± 491	0.40
CI, l/min/m^2	2.3 [1.9–3.3]	3.2 [2.8–3.9]	
Echocardiography (*n* = 26)			
TAPSE, mm	16.2 ± 7.1	17.7 ± 4.8	0.53
RV pressure, mmHg	79 ± 23	80 ± 22	0.95
TR grade			0.83
0, *n* (%)	1 (10)	2 (13)	
1, *n* (%)	3 (30)	5 (31)	
2, *n* (%)	1 (10)	0	
3, *n* (%)	5 (50)	9 (56)	
Laboratory test (*n* = 22)			
NT-proBNP, ng/l	1277 [707–2112]	1538 [313–3257]	0.74

Data are presented as *n* (%), mean ± standard deviation or median [interquartile range].

[a]Refers to no therapy or mono, dual or triple combination of prostacyclin, endothelin receptor antagonist and a phosphodiesterase type-5 inhibitor.

CI: cardiac index; DPAP: diastolic pulmonary arterial pressure; HPAH: heritable PAH; IPAH: idiopathic PAH; MPAP: mean pulmonary arterial pressure; NT-proBNP: N-terminal of the prohormone brain natriuretic peptide; PAH: pulmonary arterial hypertension; PAH-CHD: PAH associated with congenital heart disease; PAH-CTD: PAH associated with connective tissue disease; PASP: pulmonary artery systolic pressure; PCWP: pulmonary capillary wedge pressure; PVOD: pulmonary veno-occlusive disease; PVR: pulmonary vascular resistance; RV: right ventricle; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation; WHO-FC: World Health Organization functional class; 6-MWD: 6-min walk distance.

maintained clinically relevant TR mainly due to a reduction in RV dilatation and subsequent tricuspid valve annular size.

CMRI thus confirms the reversibility of severe RV dysfunction, even within several months post-LTX. This finding is in line with previous studies investigating the effects of isolated LTX for PAH [8–15] and of those of pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension [23, 24]. However, in PAH-LTX, the RV is usually exposed to increased pressure for a much longer time compared to chronic thromboembolic pulmonary hypertension pulmonary endarterectomy with respect to the time on the waiting list. In addition, previous studies in patients with isolated LTX were performed primarily in the early 1990s using echocardiography and the treatment options for PAH have greatly improved since then [4]. Although survival of patients with PAH has improved markedly with the advent of advanced treatment options, adverse RV remodelling may progress, even in patients who seem to respond to treatment [25]. Even in the present cohort with severe RV failure, the RV was able to recover consistently.

RV systolic function and dilatation are hallmark determinants of outcome in PAH, yet chronic RV pressure load results in RV myocardial stiffening and fibrosis [26–28]. Stiffening and fibrosis may be potential contributors to disease severity and outcome in PAH. Unfortunately, we had no data on myocardial fibrosis with CMRI (e.g. T1-mapping). The morphological normalization in terms of decreased RV mass and trabecular mass ratio observed in the present study may facilitate improvement in myocardial stiffening, yet remodelling patterns at the cellular level remain unknown. Several patients still had right and left atrial dilatation late after LTX, which may be a sign of residual diastolic dysfunction and/or irreversible atrial fibrosis and stiffening.

The present study demonstrated improvement in TR in all patients due to an important reduction in tricuspid annular size. Such reduction was previously demonstrated with echocardiography [13]. In our

Table 2: Cardiac magnetic resonance measurements

Measurement	Baseline (n = 10)	Post-LTX (n = 10)	Delta	P-value
RVEDVi, ml/m^2	118 ± 37	51 ± 13	-67 ± 30	<0.001
RVEF, %	32 ± 9	64 ± 9	32 ± 8	<0.001
RV mass index, g/m^2	69 ± 16	33 ± 9	36 ± 14	<0.001
RV SV/ESV	0.5 ± 0.2	1.9 ± 0.6	1.4 ± 0.5	<0.001
LVEDVi, ml/m^2	53 ± 19	61 ± 11	8 ± 15	0.11
LVEF, %	58 ± 8	62 ± 11	4 ± 12	0.28
LV mass index, g/m^2	55 ± 12	61 ± 13	6 ± 5	0.005
LV eccentricity index	2.8 ± 1.0	1.1 ± 0.1	-1.7 ± 1.0	<0.001
RV/LV volume ratio	2.3 ± 0.7	0.8 ± 0.1	-1.5 ± 0.8	<0.001
RV/LV mass ratio	1.3 ± 0.2	0.5 ± 0.1	-0.7 ± 0.2	<0.001
TV annulus diameter, mm/m^2	20.4 ± 3.5	13.3 ± 3.6	-7.0 ± 4.0	<0.001
TV annulus area, cm^2/m^2	9.8 ± 2.7	4.6 ± 1.6	-5.2 ± 2.3	<0.001

Data are presented as mean ± standard deviation.
ESV: end-systolic volume; LTX: lung transplant; LV: left ventricle; LVEF: left ventricular ejection fraction; LVEDVi: left ventricular end-diastolic volume index; RV: right ventricle; RVEDVi: right ventricular end-diastolic volume index; RVEF: right ventricular ejection fraction; SV: stroke volume; TV: tricuspid valve; SV/ESV: stroke volume/end-systolic ratio.

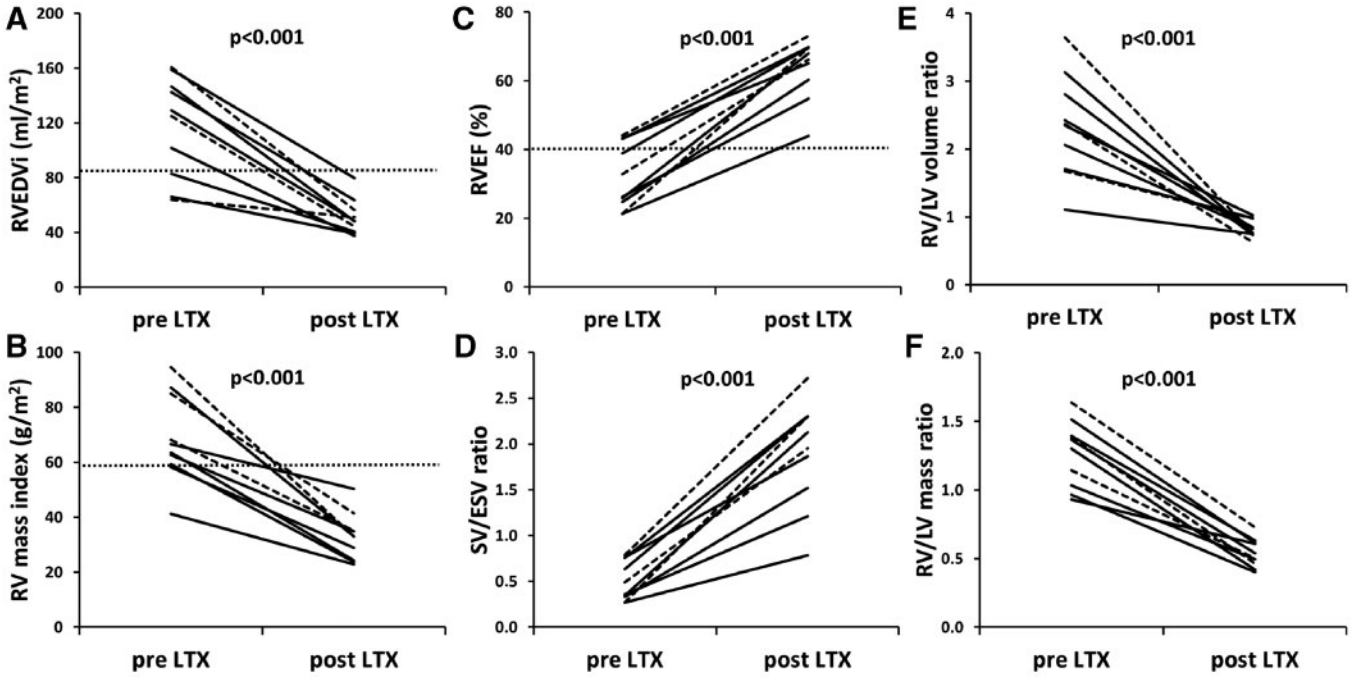

Figure 2: Right ventricular recovery. Change in CMRI measurements after LTX in patients with WHO-FC III (straight lines) and IV (dashed lines). CMRI: cardiac magnetic resonance imaging; ESV: end-systolic volume; LV: left ventricle; LXT: lung transplant; RV: right ventricle; RVEDVi: right ventricular end-diastolic volume index; RVEF: right ventricular ejection fraction; SV: stroke volume. Horizontal dotted lines represent the prognostic cut-off values in PAH for RVEDVi (i.e. 84 ml/m^2), RV mass index (i.e. 59 g/m^2) and RVEF (i.e. 40%) as previously described by Van Wolferen *et al.* [18].

study, none of the patients had undergone additional tricuspid valve repair. Tricuspid valve repair secondary to LTX may result in longer ischaemic time and additional perioperative risk. Because the tricuspid annular size normalizes due to a reduction in RV volume, we do not recommended the performance of such repair in patients who undergo isolated LTX and who have RV dilatation and severe functional TR, as previously suggested [29].

For decades, controversy has existed as to whether patients with end-stage PAH benefit more from isolated LTX than from H-LTX. Recently, comparable survival rates between patients receiving H-LTX and LTX were demonstrated [7]. However, patients requiring intensive care prior to transplant would benefit more from H-LTX than from LTX [7]. It has previously been demonstrated that VA-ECMO reduces perioperative mortality rates in patients with end-stage PAH listed for LTX [30]. In our study, 4 patients were temporarily treated with VA-ECMO postoperatively to reduce the risk of acute cardiac failure. Given the remarkable reversibility of severe RV dysfunction observed in our study, we believe that, with these improvements in perioperative care, many patients with end-stage PAH and severe RV dysfunction would still benefit from isolated LTX.

This retrospective study has several limitations. First, 8 patients who died after LTX were not included. Although these patients

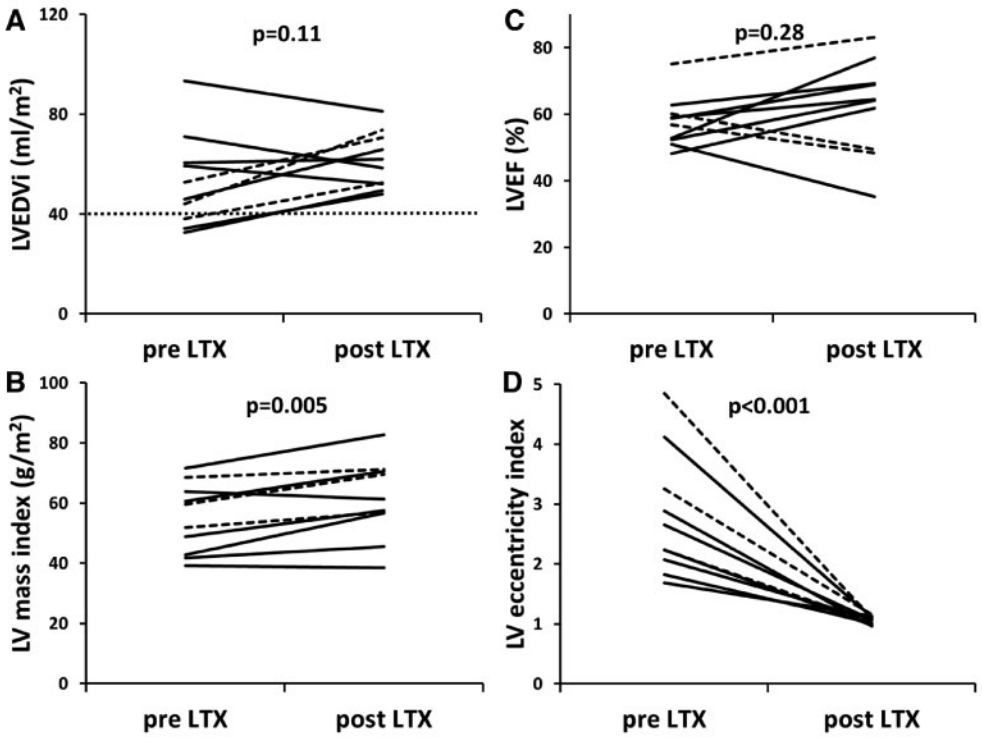

Figure 3: Left ventricular recovery. Change in cardiac magnetic resonance imaging measurements after LTX in patients with WHO-FC III (straight lines) and IV (dashed lines). LV: left ventricle; LVEDVi: left ventricular end-diastolic volume index; LVEF: left ventricular ejection fraction. Horizontal dotted line represents the prognostic cut-off for LVEDVi in patients with PAH (40 ml/m^2) [18].

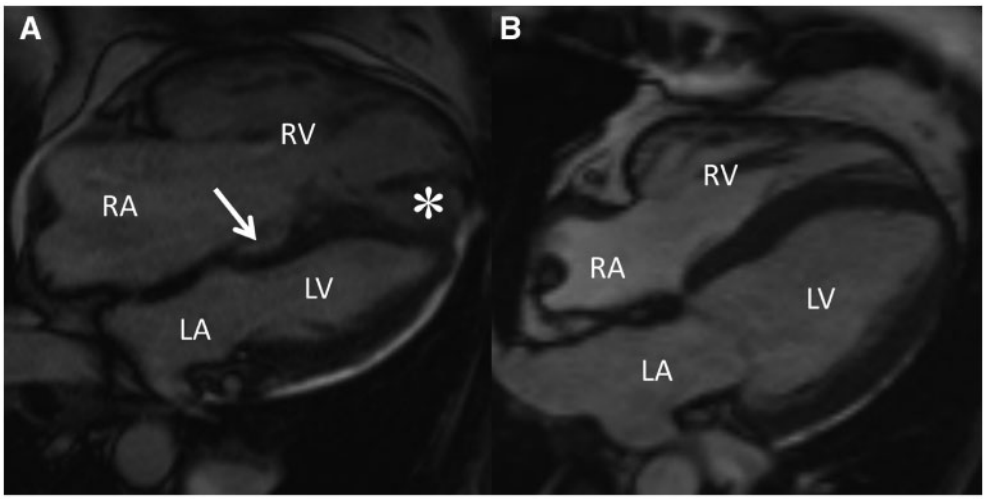

Figure 4: CMRI scans of a patient with PAH. (**A**) A typical CMRI scan from a patient with PAH. The RV and RA are severely dilated and there is septal bowing (arrow) towards the LV. (**B**) The 4-chamber CMRI scan of the same patient post-LTX. Both the RV and RA are decreased in size and interventricular septum deviation is restored. In particular, RV apical dilatation (*) is reduced post-LTX.

died of reasons other than RV failure, it is an important selection bias. The results of this study therefore apply only to patients with PAH who survive the perioperative period. Furthermore, the sample size is small. Nevertheless, results regarding RV recovery are consistent among all patients. In addition, 3 patients had an atrial septal defect closure during the transplant and 4 patients were treated temporarily with VA-ECMO postoperatively. Because of the low number of patients in subgroups, no subanalyses could be performed to compare CMRI values between these patients. CMRI studies were performed on multiple scanners. However, inter-vendor differences for quantification of ventricular function and volume using standard steady-state free-precession imaging are limited. Finally, there was a variation in interval between LTX and the postoperative CMRI. However, change in CMRI variables was not related to the duration of this interval.

In conclusion, CMRI demonstrates marked recovery of RV function and morphology after isolated bilateral LTX in a cohort

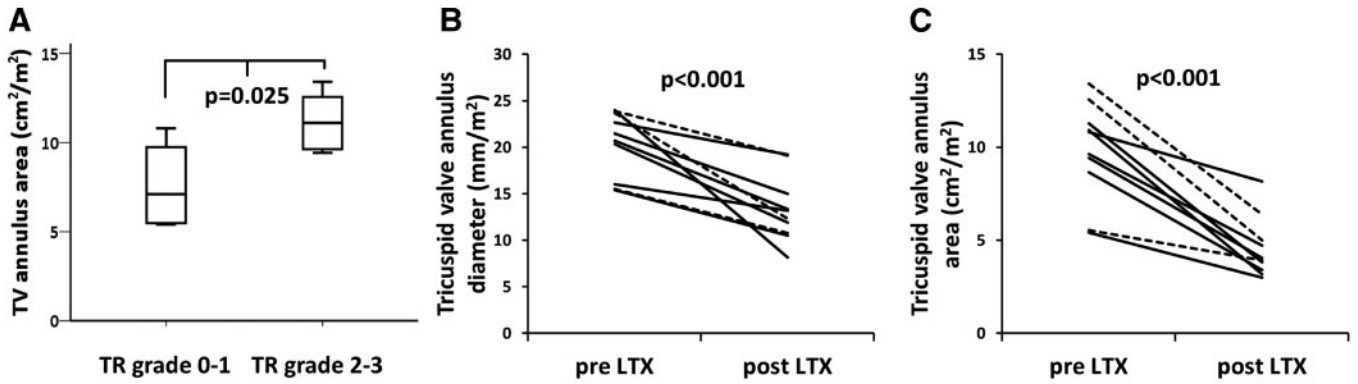

Figure 5: Tricuspid valve recovery. Measurements of the size of the tricuspid valve (TV) annulus. (**A**) Preoperative TV annulus area of patients with Grade 0 and 1 TR ($n = 4$) compared with that of patients with Grade 2 and 3 TR ($n = 6$). (**B** and **C**) Change in the diameter and the area of the TV annulus, respectively, after LTX in patients with WHO-FC III (straight lines) and IV (dashed lines).

of patients with long-standing PAH, severe RV dysfunction and inadequate ventricular-vascular coupling. In addition, left-sided parameters returned towards normal and none of the patients maintained clinically relevant TR after LTX.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

ACKNOWLEDGEMENTS

A.V.N., H.J.B. and R.M.F.B. acknowledge their support from the Netherlands Cardiovascular Research Initiative: the Dutch Heart Foundation, Dutch Federation of University Medical Centers, the Netherlands Organization for Health Research and Development and the Royal Netherlands Academy of Sciences, CVON nr. 2012-08, PHAEDRA.

Conflict of interest: A.V.N. reports speaker fees from Actelion, Glaxo Smith Kline and Pfizer, outside the submitted work. H.J.B. reports speaker fees from Actelion, Pfizer and Bayer and is part of the advisory beard of United Therapeutics and has received grant support from Boehringer Ingelheim and the Lung Foundation, outside the submitted work. The University Medical Center Groningen contracts with Actelion, Glaxo Smith Kline and Bayer for consultancy and steering committee activities by R.M.F.B., outside the submitted work. All other authors have no conflict of interest.

REFERENCES

[1] D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM *et al.* Survival in patients with primary pulmonary hypertension. results from a national prospective registry. Ann Intern Med 1991;115:343–9.

[2] Lopez Reyes R, Nauffal Manzur D, Garcia Ortega A, Menendez Salinas MA, Ansotegui Barrera E, Balerdi Perez B. Clinical characteristics and survival of patients with pulmonary hypertension: a 40-month mean follow-up. Clin Respir J 2017;11:103–11.

[3] Van de Veerdonk MC, Kind T, Marcus JT, Mauritz GJ, Heymans MW, Bogaard HJ *et al.* Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. J Am Coll Cardiol 2011;58:2511–9.

[4] Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A *et al.* 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37:67–119.

[5] Gomberg-Maitland M, Glassner-Kolmin C, Watson S, Frantz R, Park M, Frost A *et al.* Survival in pulmonary arterial hypertension patients awaiting lung transplantation. J Heart Lung Transplant 2013;32:1179–86.

[6] Fadel E, Mercier O, Mussot S, Leroy-Ladurie F, Cerrina J, Chapelier A *et al.* Long-term outcome of double-lung and heart-lung transplantation for pulmonary hypertension: A comparative retrospective study of 219 patients. Eur J Cardiothorac Surg 2010;38:277–84.

[7] Hill C, Maxwell B, Boulate D, Haddad F, Ha R, Afshar K *et al.* Heart-lung vs. double-lung transplantation for idiopathic pulmonary arterial hypertension. Clin Transplant 2015;29:1067–75.

[8] Pasque MK, Trulock EP, Kaiser LR, Cooper JD. Single-lung transplantation for pulmonary hypertension. Three-month hemodynamic follow-up. Circulation 1991;84:2275–9.

[9] Katz WE, Gasior TA, Quinlan JJ, Lazar JM, Firestone L, Griffith BP *et al.* Immediate effects of lung transplantation on right ventricular morphology and function in patients with variable degrees of pulmonary hypertension. J Am Coll Cardiol 1996;27:384–91.

[10] Globits S, Burghuber OC, Koller J, Schenk P, Frank H, Grimm M *et al.* Effect of lung transplantation on right and left ventricular volumes and function measured by magnetic resonance imaging. Am J Respir Crit Care Med 1994;149:1000–4.

[11] Ritchie M, Waggoner AD, Davila-Roman VG, Barzilai B, Trulock EP, Eisenberg PR. Echocardiographic characterization of the improvement in right ventricular function in patients with severe pulmonary hypertension after single-lung transplantation. J Am Coll Cardiol 1993;22:1170–4.

[12] Schulman LL, Leibowitz DW, Anandarangam T, DiTullio MR, McGregor CC, Smith CR *et al.* Variability of right ventricular functional recovery after lung transplantation. Transplantation 1996;62:622–5.

[13] Kasimir MT, Seebacher G, Jaksch P, Winkler G, Schmid K, Marta GM *et al.* Reverse cardiac remodelling in patients with primary pulmonary hypertension after isolated lung transplantation. Eur J Cardiothorac Surg 2004;26:776–81.

[14] Moulton MJ, Creswell LL, Ungacta FF, Downing SW, Szabo BA, Pasque MK. Magnetic resonance imaging provides evidence for remodeling of the right ventricle after single-lung transplantation for pulmonary hypertension. Circulation 1996;94:II312–9.

[15] Frist WH, Lorenz CH, Walker ES, Loyd JE, Stewart JR, Graham TP *et al.* MRI complements standard assessment of right ventricular function after lung transplantation. Ann Thorac Surg 1995;60:268–71.

[16] Haddad F, Doyle R, Murphy DJ, Hunt SA. Right ventricular function in cardiovascular disease, part II: pathophysiology, clinical importance, and management of right ventricular failure. Circulation 2008;117:1717–31.

[17] Gorter TM, van Melle JP, Freling HG, Ebels T, Bartelds B, Pieper PG *et al.* Pulmonary regurgitant volume is superior to fraction using background-corrected phase contrast MRI in determining the severity of regurgitation in repaired tetralogy of fallot. Int J Cardiovasc Imaging 2015;31:1169–77.

[18] Van Wolferen SA, Marcus JT, Boonstra A, Marques KM, Bronzwaer JG, Spreeuwenberg MD *et al*. Prognostic value of right ventricular mass, volume, and function in idiopathic pulmonary arterial hypertension. Eur Heart J 2007;28:1250–7.
[19] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L *et al*. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015;28:1–39.e14.
[20] Vanderpool RR, Pinsky MR, Naeije R, Deible C, Kosaraju V, Bunner C *et al*. RV-pulmonary arterial coupling predicts outcome in patients referred for pulmonary hypertension. Heart 2015;101:37–43.
[21] Swift AJ, Rajaram S, Capener D, Elliot C, Condliffe R, Wild JM *et al*. Longitudinal and transverse right ventricular function in pulmonary hypertension: cardiovascular magnetic resonance imaging study from the ASPIRE registry. Pulm Circ 2015;5:557–64.
[22] Lancellotti P, Moura L, Pierard LA, Agricola E, Popescu BA, Tribouilloy C *et al*. European Association of Echocardiography Recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). Eur J Echocardiogr 2010;11:307–32.
[23] Rolf A, Rixe J, Kim WK, Borgel J, Mollmann H, Nef HM *et al*. Right ventricular adaptation to pulmonary pressure load in patients with chronic thromboembolic pulmonary hypertension before and after successful pulmonary endarterectomy—a cardiovascular magnetic resonance study. J Cardiovasc Magn Reson 2014;16:96.
[24] Claessen G, La Gerche A, Dymarkowski S, Claus P, Delcroix M, Heidbuchel H. Pulmonary vascular and right ventricular reserve in patients with normalized resting hemodynamics after pulmonary endarterectomy. J Am Heart Assoc 2015;4:e001602.
[25] Van de Veerdonk MC, Marcus JT, Westerhof N, de Man FS, Boonstra A, Heymans MW *et al*. Signs of right ventricular deterioration in clinically stable patients with pulmonary arterial hypertension. Chest 2015;147:1063–71.
[26] Aguero J, Ishikawa K, Hadri L, Santos-Gallego C, Fish K, Hammoudi N *et al*. Characterization of right ventricular remodeling and failure in a chronic pulmonary hypertension model. Am J Physiol Heart Circ Physiol 2014;307:H1204–15.
[27] Borgdorff MA, Koop AM, Bloks VW, Dickinson MG, Steendijk P, Sillje HH *et al*. Clinical symptoms of right ventricular failure in experimental chronic pressure load are associated with progressive diastolic dysfunction. J Mol Cell Cardiol 2015;79:244–53.
[28] Rain S, Handoko ML, Trip P, Gan CT, Westerhof N, Stienen GJ *et al*. Right ventricular diastolic impairment in patients with pulmonary arterial hypertension. Circulation 2013;128:2016–25, 1–10.
[29] Shigemura N, Sareyyupoglu B, Bhama J, Bonde P, Thacker J, Bermudez C *et al*. Combining tricuspid valve repair with double lung transplantation in patients with severe pulmonary hypertension, tricuspid regurgitation, and right ventricular dysfunction. Chest 2011;140:1033–9.
[30] Garcia Saez D, Zych B, Mohite PN, Simon AR. Transplantation of lungs after ex vivo reconditioning in a patient on semi-elective long-term veno-arterial extracorporeal life support. Eur J Cardiothorac Surg 2014;45:389–90.