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Early post-transplant elevated pulmonary artery pressure predicts adverse outcome in cardiac recipients

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ABSTRACT

Aim: To investigate the prognostic value of early post-transplant hemodynamic measurements on 5-year mortality in cardiac recipients (HTx).
Methods: A right heart catheterization was performed in 290 heart transplantation (HTx) recipients at a one-year post-HTx evaluation. To study the effect of post-HTx hemodynamic variables on 5-year outcome, the cohort was stratified into several subgroups. For right atrial pressure (RAP), mean pulmonary artery pressure (MPAP), pulmonary artery wedge pressure (PAWP), and pulmonary vascular resistance (PVR), patients with values from the upper 10th percentile (high), were compared with those with values from the remaining lower 90th percentile (normal). For cardiac index (CI), patients with values from the lower 10th percentile (low) were compared with those with values from the remaining upper 90th percentile (normal).
Results: Death or re-transplantation within 5 years after the one-year control occurred in 44 patients (13%). Of those, death or re-HTx was related to graft failure in 20 of cases (45%) and non-cardiac causes in 24 of cases (55%). The risk of death or re-HTx was higher in the subgroup with MPAP above 23 mmHg than those equal to or below this value [hazard ratio 3.22, 95% confidence interval (CI) 1.49–6.97; $P = 0.003$]. The association remained significant despite adjustment for several comorbidities. There were no differences in outcome between subgroups stratified with respect to high versus low RAP, PAWP, CI or PVR.
Conclusion: Elevated pulmonary artery pressure at a first annual evaluation after HTx was the only hemodynamic variable that predicted impaired outcome in cardiac recipients.

1. Introduction

Heart transplantation (HTx) is the treatment of choice for selected patients with advanced heart failure. Over the last decades, therapeutic advances have included improved donor management and heart preservation, better understanding of donor-recipient mismatch, and development of new immunosuppressive strategies [1]. The survival of transplant recipients approaches 86% at 1 year, 77% at 5 years and 63% at 10 years [2], which is superior to the expected less than 50% one-year survival observed in medically treated heart failure patients in NYHA class IV [3–5].

Of importance for this development is the identification of pre- and post-transplant risk factors for poor outcome, which has brought about preventive and therapeutic measures resulting in improved survival. One example is the significance of invasive hemodynamic assessment with a right heart catheterization (RHC) during evaluation for heart transplantation. Pulmonary hypertension (PH) with a high pulmonary vascular resistance (PVR) unresponsive to vasodilation is strongly related to early graft failure and, therefore, a contraindication to heart transplantation [6]. To detect a high PVR prior to HTx, the International Society for Heart and Lung Transplantation (ISHLT) repeated RHC during HTx waiting time [6].

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For surveillance after heart transplantation the value of invasive hemodynamic assessment is less clear. Previous data suggest that residual early post-transplant PH or high PVR may be related to impaired prognosis [7,8], but the significance of other hemodynamic measurements is unknown. At our institution, we perform RHC as a routine investigation at one-year follow-up after heart transplantation. We aimed to investigate the prognostic value of one-year post-HTx hemodynamic measurements on mortality and graft failure during a 5-year follow-up.

2. Methods

2.1. Study population

All patients receiving heart transplantation (n = 491) between 1988 and 2009 at Sahlgrenska University Hospital were screened for this study. Children under the age of 18 years, (n = 58), patients with incomplete data (n = 29) and those who died (n = 98) or were re-transplanted (n = 16) before the one-year follow-up was performed were excluded from the analysis. This resulted in a final study cohort comprising 290 patients, who were all followed for five years (Supplementary Fig. 1).

Listing criteria for heart transplantation were coherent with established international guidelines [6]. Recipients and donors were matched for ABO blood group type compatibility and body size. Complement-dependent cytotoxicity assays were performed to assess the ability of recipient serum to lyse a panel of T or B cells and, if positive above a certain level, a prospective donor-specific cross-match was performed.

The study was conducted in accordance with the amended Declaration of Helsinki and was approved by the Institutional Review Board at the University of Gothenburg. All patients gave written informed consent prior to surgery to have their data collected in a transplant registry for care management and research purposes.

2.2. Immunosuppression

We have applied induction therapy throughout our HTx program, in most cases anti-thymocyte globulin (ATG). As maintenance therapy all patients have received a calcineurin inhibitor (cyclosporine or tacrolimus), an anti-metabolite (azathioprine or mycophenolate mofetil [MMF]), and prednisolone. Percutaneous transvenous endomyocardial biopsies for the purpose of rejection monitoring have been used during the first post-operative year, thereafter only when a rejection is clinically suspected. After the introduction of tacrolimus and MMF as first-line immunosuppressive treatment, prednisolone is on most cases tapered and withdrawn during the first year.

2.3. Data collection

Clinical data from the preoperative work–up, the time of heart transplantation, and the follow-up period were collected retrospectively and recorded in a database. Demographic variables included age, gender, height, weight, body mass index, pre-transplant co-morbidities (diabetes mellitus, hypertension, history of tobacco use, cytomegalovirus serology). During the first year of follow-up data on immunosuppressive treatment and rejections were registered. Results from a right heart catheterization, an echocardiography and a coronary angiography at a one-year post-HTx follow-up were collected. We used the ISHLT guidelines to classify the degree of cardiac allograft vasculopathy (CAV) [9].

Mortality was assessed based on data from the Swedish National Death Registry and information regarding cause of death was ascertained based on Death Certificates. The study end-point was defined as mortality or re-transplantation during five years following the first yearly follow-up control, i.e. during one to six years after HTx. All patients were followed for five years with respect to these end-points.

2.4. Stratification of the patient cohort and follow-up

In order to study the relation between post-transplant hemodynamic variables, on the one hand, and graft endurance and total survival, on the other, the study cohort was stratified into different subgroups or strata based on right atrial pressure (RAP), mean pulmonary artery pressure (MPAP), mean arterial pressure (MAP), pulmonary artery wedge pressure (PAWP) and pulmonary vascular resistance (PVR). The survival of patients and grafts from those with values from the upper 10th percentile (high) was compared with the remaining lower 90th percentile (normal). For cardiac index (CI), patients with values from the lower 10th percentile (low) were compared with those with values from the remaining upper 90th percentile (normal).

2.5. Statistical analysis

All the statistical analyses were performed with IBM SPSS statistics version 23. Data are presented as means and standard deviations or numbers and percentages. Differences in the mortality and re-transplantation between subjects with high MPAP and normal MPAP were investigated using general linear models (GLM). This was performed in a primary unadjusted analysis and, thereafter, in a secondary analysis adjusted for age, sex of the recipient, and age of the donor. The association between other hemodynamic parameters at one-year follow-up and mortality was investigated with Kaplan-Meier curves and Cox proportional regression, after adjusting for relevant covariates.

3. Results

Baseline characteristics and pre-HTx hemodynamics for the total study group and for those with high (upper 10th percentile) and normal (lower 90th percentile) post-HTX MPAP at one-year control are presented in Table 1. The cut-off for high MPAP was found to be > 23 mmHg and this group included patients that were older, more obese, displayed higher pre-HTx pulmonary pressure, and had more often heart failure of ischemic etiology, as compared with those who had post-HTx pulmonary pressures $\leq$23 mmHg. Apart from a higher MPAP, pre-transplant hemodynamics were quite similar in the two groups.

Supplementary Fig. 2 shows Kaplan-Meier estimates for freedom from death or re-transplantation in heart transplant candidates with a high, but reversible, versus normal pulmonary vascular resistance (PVR) observed during pre-HTx evaluation. The 5-year survival in patients with a PVR above 3 WU (reversible) did not differ from that observed in patients with a PVR below or equal to 3 WU.

Table 2 displays hemodynamic measurements, left ventricular ejection fraction (LVEF), coronary artery vasculopathy (CAV) and rejections at one-year control after HTx. Patients with high post-HTx MPAP displayed higher MAP, CVP, PAWP, and PVR, as compared with those with normal post-HTx pulmonary pressure. HR and CI, on the other hand, did not differ between groups. There were no significant differences between the groups with respect to LVEF, CAV; or treated cellular rejections during the first year.

Fig. 1 shows that the proportion of death or re-transplantation during a 5-year follow-up was significantly higher in patients with high MPAP (32% [No = 9]) as compared with those with normal MPAP (13% [No = 35]) (p = 0.009). The percentage of patients who

Table 1
Baseline characteristics for the total study group and for those with high (upper 10th percentile) and normal (lower 90th percentile) post-HTx MPAP.

	All patients (n = 290)	Post-HTx MPAP > 23 mmHg (n = 28)	Post-HTx MPAP ≤ 23 mmHg (n = 262)	P-Value
Recipient characteristics				
Age (years)	48 ± 11	52 ± 9	48 ± 12	0.033
Male sex	224 (77)	25 (89)	199 (76)	0.11
BMI (kg/m^2)	25 ± 4	27 ± 5	25 ± 4	0.002
History of smoking	180 (62)	15 (54)	165 (63)	0.072
Previous hypertension	37 (13)	6 (21)	31 (12)	0.148
Diabetes	30 (10)	2 (7)	28 (11)	0.558
Ischemic heart disease	93 (32)	14 (50)	80 (31)	0.037
Donor characteristics				
Age (years)	36 ± 14	39 ± 16	36 ± 13	0.261
Male sex	202 (70)	23 (82)	179 (68)	0.131
Ischemic time (min)	179 ± 50	188 ± 65	178 ± 48	0.318
Pre-transplant hemodynamic measurements				
HR (bpm)	81 ± 19	77 ± 15	81 ± 20	0.363
MPAP (mmHg)	32 ± 9	37 ± 8	32 ± 9	0.007
MAP (mmHg)	74 ± 11	72 ± 10	75 ± 12	0.446
RAP (mmHg)	10 ± 7	9 ± 4	10 ± 7	0.404
PAWP (mmHg)	23 ± 7	24 ± 8	22 ± 7	0.280
CO (L/min)	3.7 ± 1.0	4.1 ± 1.1	3.7 ± 1.0	0.035
CI (L/min/m^2)	1.9 ± 0.5	2.1 ± 0.5	1.9 ± 0.5	0.312
PVR (WU)	2.9 ± 1.7	3.4 ± 1.9	2.9 ± 1.6	0.107
SVR (WU)	19 ± 6	16 ± 5	19 ± 6	0.142

Values are means ± standard deviation or percentages.
BMI: body mass index; HR: heart rate; MPAP: mean pulmonary artery pressure; MAP: mean arterial pressure; RAP: right atrial pressure; PAWP: pulmonary artery wedge pressure; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance; SVR: systemic vascular resistance

Table 2
Hemodynamic measurements, ejection fraction, and presence of CAV at one-year follow-up after heart transplantation in all patients and in those with high vs low post-HTx mPAP.

	All patients (n = 290)	Post HTx mPAP > 23 mmHg (n = 28)	Post HTx mPAP ≤ 23 mmHg (n = 262)	P-Value
HR (bpm)	86 ± 13	87 ± 16	86 ± 13	0.716
mPAP mmHg	17 ± 5	27 ± 4	16 ± 4	<0.001
MAP mmHg	105 ± 15	111 ± 15	105 ± 15	0.045
RAP mmHg	3.1 ± 2.8	6.2 ± 3.5	2.8 ± 2.5	<0.001
PAWP mmHg	8.0 ± 4.0	13 ± 5	7.5 ± 3.6	<0.001
CO L/min	6.1 ± 1.3	6.7 ± 1.3	6.0 ± 1.3	0.014
CI L/min/m^2	3.2 ± 0.7	3.3 ± 0.7	3.2 ± 0.7	0.234
PVR (WU)	1.5 ± 0.7	2.2 ± 0.8	1.5 ± 0.6	<0.001
SVR (WU)	18 ± 5	16 ± 4	18 ± 5	0.151
LVEF (%)	64 ± 8	64 ± 8	62 ± 9	0.168
CAV 0/1 (vs 2/3)	251 (87)	24 (86)	287 (87)	0.891
Rejections ≥ 2R during year 1	283 (75)	21(77)	191 (74)	0.819

Values are means ± standard deviation or Numbers (percentages).
HR: heart rate; MPAP: mean pulmonary artery pressure; MAP: mean arterial pressure; RAP: right atrial pressure; PAWP: pulmonary artery wedge pressure; CO: cardiac output; CI: cardiac index; PVR: pulmonary vascular resistance; SVR: systemic vascular resistance; LVEF: Left ventricular ejection fraction; CAV: cardiac allograft vasculopathy.

died from non-cardiac caused were higher in the high MPAP group (17.8%) as compared with those in the low MPAP group (7.3%). This was also the case for graft failure (14.3% versus 6.1%), but the differences between these subgroups were not statistically significant.

Fig. 2 displays Kaplan-Meier curves for freedom from death or re-transplantation in different subgroups stratified with respect to hemodynamic measurement at one-year follow-up: high (upper 10th percentile) versus normal (lower 90th percentile) MPAP, MAP, RAP, PAWP and PVR; and low (lower 10th percentile) versus normal (upper 90th percentile) CI. Only elevated MPAP was significantly associated with poor long-term outcomes, P < 0.001 (Panel A). However, there was no difference in survival between patient subgroups stratified with respect to high versus low MAP, RAP, PAWP, CI, or PVR.

In Table 3 a univariate Cox analysis shows the association between risk of death or re-transplantation and selected characteristics during 5-year follow-up after the first annual post-HTx follow-up. Only MPAP as a continuous variable was significantly associated with adverse outcome. An increase of 1 mmHg in MPAP raised the mortality rate with 11% during the 5 years follow-up. Further analyses describing the association between MPAP and death or re-transplantation are shown in Table 3. When MPAP was dichotomized in high and normal levels the univariate Cox regression analysis showed that patient with MPAP above the 10th percentile had worse survival that those with MPAP in the lower 90th percentile (HR 3.6 CI 1.3–11 p = 0.017). The association between high MPAP and mortality was still significant after adjustments in the full model including age, smoking habits, diabetes, hypertension, ischemia time, cause of transplantation, ejection fraction, CAV, pre-transplantation MPAP, PAWP and the age of the donor. Similar finding appeared when applying pulmonary artery pressure as a continuous variable in the different models.

The characteristics of study participants based on death or re-transplantation versus event-free survival during 5-year follow-up after first annual evaluation are displayed in Supplementary

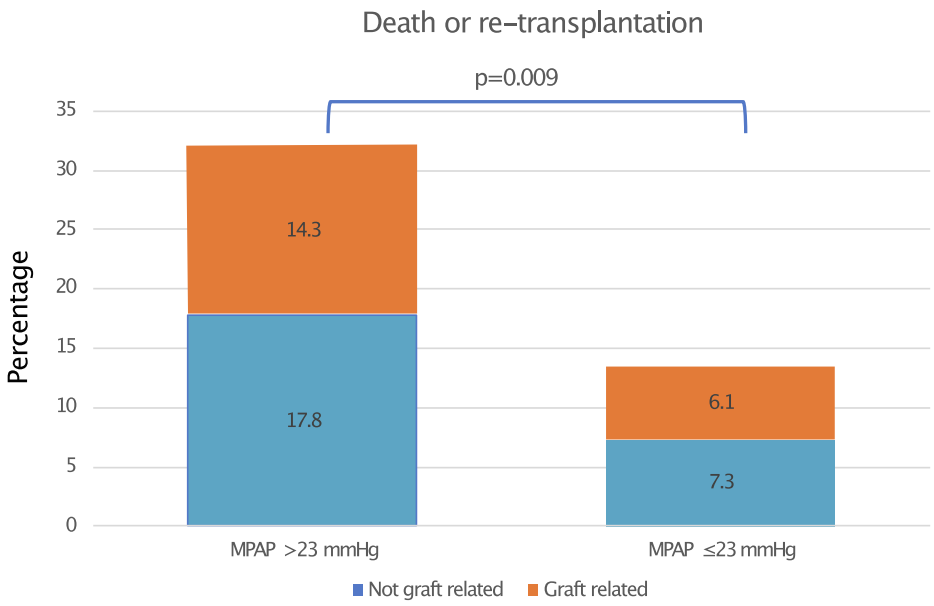

Fig. 1. Percentage of death or re-transplantations among patients with MPAP ≥ 23 mmHg as compared to those with MPAP < 23 mmHg at one-year post-HTx follow-up.

Table 2. Apart from a higher MPAP and PVR at one-year post-HTx follow-up there were virtually no differences between survivors and non-survivors.

4. Discussion

The main finding of the present study is that heart transplant recipients who displayed an elevated MPAP at one-year after HTx had worse outcome during a 5-year follow-up as compared to those with lower values. A mild elevation of MPAP predicted impaired survival or re-transplantation independent of age, higher body mass index and ischemic etiology. This relationship remained stable, even after adjustment for several important hemodynamic and comorbid characteristics. No other hemodynamic variable obtained at the one-year post-HTx follow-up correlated to adverse outcome. Although not statistically significant, patients with elevated MPAP had higher rates of both graft-related and non-graft-related mortality and re-transplantation.

Our results are in line with the findings of Goland et al. [8] and Gude et al. [7], who reported an association between post-HTx pulmonary hypertension and impaired outcome. However, the definition of pulmonary hypertension (PH) in these studies was different from ours. Goland et al. used PVR > 3 WU or a transpulmonary gradient > 10 mmHg as a cut-off for the definition of PH, while Gude et al. defined PH as MPAP ≥ 20 mmHg [10,11]. According to international guidelines [12] the definition of pulmonary hypertension is MPAP ≥ 25 mmHg, but only a limited number of subjects in the present study met that criteria. Therefore, we stratified the study population, and compared the values from the upper 10th percentile (MPAP ≥ 23 mmHg), with those from the remaining lower 90th percentile. We also found that MPAP as a continuous variable showed a strong and independent association with impaired survival, suggesting that even moderately elevated MPAP values are of importance with respect to outcome.

In recent years there has been a vivid discussion on the importance of "borderline MPAP values" defined as MPAP between 20 and 25 mmHg, which are values above the upper limit of normal, but not fulfilling the current criteria of PH (≥25 mmHg) [10,11]. Published data suggests that borderline MPAP hypertension is a clinically relevant condition, which may be caused by several factors, including vascular and /or parenchymal pulmonary disease, as well as left heart disease or sleep-related breathing disorders [13–15]. Patients with this condition have decreased exercise capacity and an increased risk of hospitalization and mortality compared to patients with normal resting hemodynamics. Thus, borderline elevation of MPAP may be a marker of poor prognosis [10,11,15,16]. At present, the natural history of such modest elevation of MPAP in the context of other clinical conditions is poorly defined. Our results add to the current knowledge concerning the importance of borderline elevation of pulmonary artery pressure in patients after HTx.

In the present study, heart transplant candidates with a high but reversible PVR (≥3 WU) at pre-transplant evaluation did not suffer from worse outcomes compared to those with normal PVR (<3 WU). Still patients with elevated pre-HTx pulmonary pressures had higher post-HTx pulmonary pressure, indicating that remodeling of the pulmonary vascular bed was not fully reversible after transplantation. Studies from the early era of HTx showed that pre–transplant pulmonary hypertension due to elevated PVR was a risk factor for both short- and long-term mortality after HTx [17–19]. Therefore, a PVR above 5 Wood units and lack of response to vasodilator testing has been considered to be an absolute contraindication to HTx [6]. Our findings concur with previous reports showing that pre-transplant PVR elevation that can be reversed by vasodilator testing does not affect long-term survival after HTx [7,8,20].

The development of a restrictive ventricular filling pattern is not uncommon after HTx [21,22]. The clinical picture is characterized by increasing filling pressures and reduced exercise capacity, or other heart failure symptoms, despite normal systolic function. The cause of this post-transplant phenomenon is unclear and probably multifactorial [22,23]. We had expected that increased filling pressures consistent with a restrictive ventricular physiology and/or reduced cardiac index, suggesting poor tissue perfusion, would predict poor outcomes. However, the rate of rejection and vasculopathy at one year was uncommon, which could explain why neither filling pressures nor cardiac index were related to outcome. Ciftci et al. [24] reported a close correlation between and acute rejection posttransplant PH and death. In our study, patients that died or were re-transplanted during the first year were excluded from analysis, which may constitute a selection bias in this context.

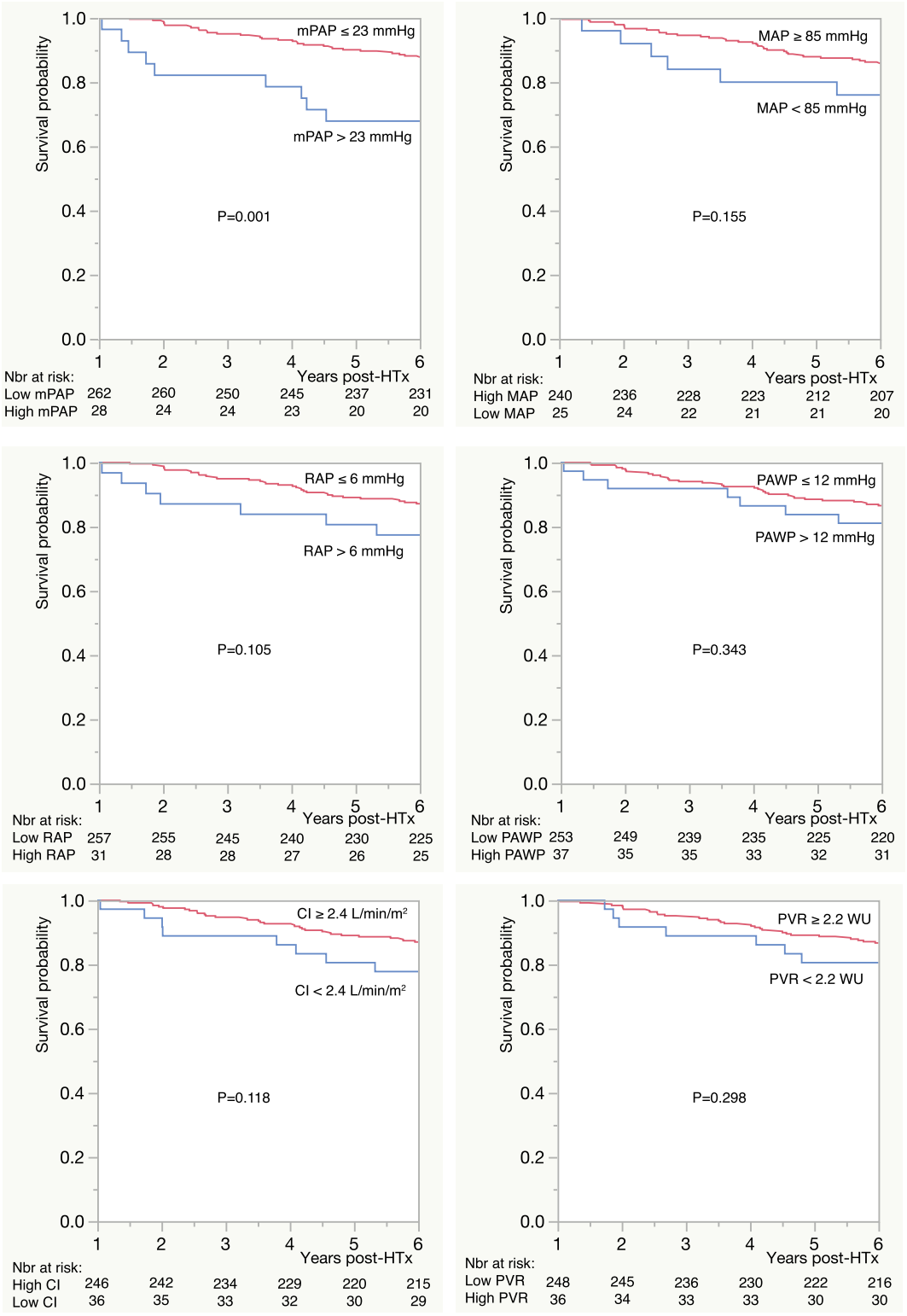

Fig. 2. Kaplan-Meier curves for freedom from death or re-transplantation in different subgroups stratified with respect to hemodynamic measurements at one-year post HTx.

In a recently published study by Skibsted Clemmensen et al. [25], only invasively measured RAP along with decreased RV-free wall global longitudinal strain offered prognostic information in predicting 5-year outcomes after HTx. (defined as a composite of cardiovascular mortality, re-HTx and heart failure hospitalization). Notably, MPAP at one year did not predict outcomes. However, it is difficult to compare these results with our findings since the adverse outcomes in that study were mainly driven by hospitalization due to heart failure, which was not studied by us.

Somewhat surprisingly, excessive deaths in patients with post-transplant elevated pulmonary artery pressure were related to an increase in both cardiac and non-cardiac causes. Although we do not have any obvious explanations to these findings, we could speculate that the presence of post-transplant pulmonary hyper-

Table 3
Cox proportional-hazards models for the association between the risk of death or re-transplantation and PH < 23 mmHg and MPAP during 5-year follow-up after first annual post-HTx evaluation.

	Hazard ratio	Confidence interval	p-value
Pulmonary hypertension (MPAP > 23 mmHg)			
Model 1	3.22	1.49–6.97	0.003
Model 2	2.95	1.24–6.99	0.014
Model 3	3.04	1.22–7.54	0.017
Mean pulmonary artery pressure			
Model 1	1.09	1.03–1.16	0.005
Model 2	1.11	1.03–1.20	0.007
Model 3	1.13	1.02–1.21	0.006

Model 1: Adjusted for age, sex and age of donor.
Model 2: Adjusted for age, sex, age of donor and PAWP.
Model 3: Adjusted for age, sex, age of donor, PAWP, mPAP (pre-HTx), Diagnosis, Smoking, HT, DM, ischemic time, and CAV.
MPAP: mean pulmonary artery pressure; PAWP pulmonary artery wegde pressure; HT: hypertension; DM: diabetes mellitus; CAV: cardiac allograft vasculopathy

tension is a marker of a less adaptive circulation or render patients more susceptible for pulmonary infections. Also, increased vascular reactivity in the pulmonary circulation could be a bystander or a consequence of other extra-cardiac disease processes. In a recent systematic review and meta-analysis by Kolte et al. [26], patients with mild PH, defined as a MPAP > 19 mmHg, had a 19% increased risk for death over 5 years. Although speculative, we suggest that mildly elevated pulmonary artery pressure, indicating a mismatch between cardiac output and pulmonary vascular resistance, may be a marker for several different pathophysiological processes, also in the post-HTx population. Therefore, such patients should undergo more extensive surveillance with respect to rejection processes and extracardiac diseases.

4.1. Strengths and limitations

This longitudinal study was based on the largest HTx database in Sweden. Detailed information on patients could be obtained, which allowed for multivariable analyses and adjustments for several potential confounders. However, a residual confounding effect cannot be excluded. All measurements were performed in the same hospital and using the same technique and missing hemodynamic data occurred only in a limited number of cases. The use of validated registry data in Sweden allowed a complete (100%) follow-up of the study population with respect to endpoints.

The observational and retrospective nature of the study, as well as the low numbers of evens, does not permit conclusions on causality. Further experimental studies on the field are needed to clarify the association between elevated pulmonary artery pressure and all-cause mortality.

5. Conclusion

In this large Swedish cohort of heart transplant recipients, the presence of mild elevation of pulmonary artery pressure at one year after HTx was associated with increased mortality and re-transplantation over five-years. Thus, an invasive hemodynamic investigation early after HTx appears to carry valuable prognostic information and motivates more extensive clinical surveillance in those with elevated pulmonary artery pressure.

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Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2019.100438.

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