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ORIGINAL ARTICLE

Is the transpulmonary pressure gradient a predictor for mortality after orthotopic cardiac transplantation?

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Summary

Elevated pulmonary vascular resistance (PVR) is a well-known risk factor for right ventricular failure after orthotopic cardiac transplantation. The influence of preoperative transpulmonary pressure gradient (TPG) and PVR on post-transplant 30 days mortality was evaluated. To analyze the response of PVR and TPG to cardiac transplantation, we analyzed 718 adult patients undergoing primary cardiac transplantation. Indications for operation were: 35.2% ischemic cardiomyopathy (ICM), 61.2% idiopathic dilated cardiomyopathy (DCM), and 3.3% other diagnosis (e.g. hypertrophic cardiomyopathy). The mean age (51.9) and the mean ischemic time (169.7 min) were comparable between 30 days survivors and nonsurvivors. Student's *t*-tests and chi-square analysis were used to compare data from 30-day survivors and nonsurvivors. Statistical significance was defined as $P < 0.05$. Fisher's exact test and multiple logistic regression analysis was performed to evaluate the relationship between hemodynamic parameters and outcome after transplantation. Primary end-point was 30 days mortality and secondary end-point long-term survival of patient groups with different TPG and PVR values. In survivors the mean TPG was 10.3 ± 5.1 (mean ± SD) vs. 13 ± 6.6 in patients who died after transplantation ($P = 0.0012$). The PVR was 2.6 ± 1.4 vs. 3.5 ± 2.2 ($P = 0.0012$). In multivariate logistic regression, the parameters TPG and PVR exhibit a significant influence between survivors and nonsurvivors after cardiac transplantation within 30 days (TPG: $P = 0.0012$; PVR: $P = 0.0012$). The mortality rates in patients with TPG > 11 mmHg and PVR < 2.8 Wood units or TPG < 11 mmHg and PVR > 2.8 Wood units were comparable to those with TPG < 11 mmHg and PVR < 2.8 mmHg. The TPG is an important predictor in nonrejection-related early mortality after orthotopic cardiac transplantation. The determination of TPG in combination with PVR is a more reliable predictor of early post-transplant survival than PVR alone.

Introduction

Cardiac transplantation is an established and highly effective procedure for patients with end-stage heart disease. Right ventricular failure of the allograft because of severe pulmonary hypertension is a common problem after heart transplantation. The right ventricle of the donor is not adapted to the elevated pulmonary pressure of the patient and therefore not able to function effectively. The clinical measure of preoperative pulmonary hypertension has been pulmonary vascular resistance (PVR), which has been used to identify the risk of right heart failure in the early postoperative period in many centers. Another important parameter that characterizes the severity of pulmonary

hypertension is the transpulmonary pressure gradient (TPG). High PVR and elevated TPG have been associated with an increased early postoperative mortality after orthotopic transplantation. The aim of this analysis was to investigate the influence of the TPG compared with PVR on perioperative outcome after orthotopic cardiac transplantation.

Methods

Patient population

From November 1984 through March 2001, a total of 735 adult patients underwent heart transplantation at the General Hospital Vienna. Demographic, clinical, and hemodynamic parameters were retrospectively reviewed. Complete preoperative and postoperative clinical and hemodynamic data, which allowed evaluation of the association between perioperative mortality and the pulmonary hemodynamic indices PVR, TPG, mean pulmonary artery pressures (MPAP) and pulmonary capillary wedge pressures (PCWP), were available in 718 patients. The primary end-point of the study was the 30-day mortality caused by donor heart failure. Patients below 18 years of age, retransplantations, and graft failure caused by acute or hyperacute rejection were excluded.

Cardiac catheterization

In patients referred for evaluation of orthotopic heart transplantation, right heart catheterization was performed using standard balloon tipped pulmonary artery catheters from the right jugular vein approach. Preoperative hemodynamic data included only data obtained without specific attempts to alter the PVR by inotropic or vasodilator infusion protocols. The parameters measured included body surface area (BSA) calculated from height and weight, MPAP, and mean PCWP. Cardiac output (CO) was measured by the thermodilution technique and cardiac index (CI) was calculated from the CO and BSA.

The PVR and TPG were calculated by means of following formulas:

$$\mathrm{PVR(Wood\ units)} = \frac{\mathrm{MPAP(mmHg)} - \mathrm{PCWP(mmHg)}}{\mathrm{CO(l/min)}}$$

$$\mathrm{TPG(mmHg)} = \mathrm{MPAP(mmHg)} - \mathrm{PCWP(mmHg)}$$

The PVR concept is the hemodynamic analog to Ohm's law ($R = \mathrm{P/Q}$) for electrical systems, which relates current flow to voltage drop in a nonreactive circuit. But there is a basic difference between the physiologic hydraulic system and the human circulation where the basic assumption of a 'nonreactive circuit' is violated. The calculated value of PVR may change under various physiologic conditions.

The PVR may not fully represent all the forces opposing flow through the pulmonary vascular bed, as it does not account for inertia, vascular compliance, and extravascular forces such as alveolar pressure [1]. Therefore, the calculated PVR can be lowered by increasing flow or CO, but the TPG (=MPAP – mean PCWP) may still be high because it is flow independent. The TPG is a flow-independent variable, as increases in pulmonary flow will distend the vessels by increasing transmural pressure, thereby diminishing PVR without altering TPG [2].

Statistics

Student's *t*-tests and chi-square analysis were used to compare data from 30-day survivors and nonsurvivors. For purposes of analysis, patients were classified into groups based on the level of preoperative PVR and TPG.

The relationship between hemodynamic parameters and outcome after transplantation was evaluated by Fisher's exact test. Multiple logistic regression analysis was performed with 30-day survival as the dependent variable and with PVR and TPG as independent variables.

Receiver operating characteristic (ROC) curves represents a test result on a continuous scale with more than one possible threshold value to define a positive or negative result [3]. ROC curves were generated by plotting sensitivity on the ordinate and specificity on the abscissa with the use of individual pulmonary hemodynamic indices for the prediction of 30-day mortality. For some analysis, patients were classified into groups based on the level of preoperative PVR and TPG, where the cutoff were defined as the points in the ROC plots where sensitivity equals specificity. All tests were two-sided and statistical significance was defined as $P < 0.05$. The statistical package used was SAS 8.1 (SAS Institute Inc, Cary, NC, USA). Actuarial survival analysis was calculated by means of Kaplan–Meier analysis.

Results

The demographic and clinical characteristics of 718 patients who underwent orthotopic heart transplantation are shown in Table 1. Seventy patients (9.75%) of this cohort died within 30 days after transplantation because of primary graft failure. No statistically significant differences were detected between survivors and nonsurvivors on the basis of sex, recipient age, indication for transplantation, ischemic time, or sex mismatch. The donor age showed statistical significance ($P = 0.0146$). Preoperative

Table 1. Demographic and clinical profile of the entire cohort and of 30-day survivors and nonsurvivors.

	Entire cohort ($n = 718$)	Survivors ($n = 648$)	Nonsurvivors ($n = 70$)	*P*-value
Male	469 (69.9)	450 (70.3)	19 (61.3)	0.2955
Recipient age (mean ± SD)	51.9 ± 10.1	51.8 ± 9.7	53.4 ± 8.7	0.4644
Donor age (mean ± SD)	33.3 ± 11.7	33.9 ± 11.4	44.7 ± 13.9	0.0146
Ischemic time (min)	169.7 ± 56.9	168.6 ± 55.8	186.4 ± 65.8	0.193
Sex mismatch	25.9%	25.7%	29%	0.678
Indication for transplantation				
Coronary artery disease	236 (35.2)	224 (35)	12 (38.7)	0.702
Idiopathic cardiomyopathy	413 (61.6)	394 (61.6)	19 (61.3)	0.976
Other	22 (3.3)	22 (3.4)	0 (0)	0.617

P-value reflects two-sided Fishers exact test comparing survivors versus nonsurvivors.
Values in parentheses expressed as percentage.

hemodynamic data are shown in Table 2. The transpulmonary gradient, pulmonary artery pressure, and MPAP all revealed statistical significance between survivors and nonsurvivors.

We divided patients who died within 1 month because of right heart failure into four hemodynamic groups based on cutoff values of the ROC curve. The cutoff were derived from a diagonal line crossing the ROC curve and resulted in 2.8 Wood units for the PVR and 11 mmHg for the TPG (Fig. 1). The entire cohort was divided into patients with TPG > 11 mmHg and PVR > 2.8 Wood units (group D, $n = 258$) compared to those with TPG <11 mmHg and PVR < 2.8 Wood units (group A, $n = 354$). Group D had a significantly higher early mortality rate as group A ($P = 0.017$). Patients were further grouped into hemodynamic subsets with TPG < 11 mmHg and PVR > 2.8 Wood units (group B, $n = 56$) as well as TPG > 11 mmHg and PVR < 2.8 Wood units (group C, $n = 50$, Table 3). Comparing the early death in patient groups with TPG < 11 mmHg and variable PVR (groups A + B) no statistical differences were revealed ($P = 0.573$, Fig. 2).

Table 2. Preoperative hemodynamic profiles (mean ± SD).

	Entire cohort ($n = 718$)	Survivors ($n = 648$)	Nonsurvivors ($n = 70$)	*P*-value
SPAP (mmHg)	49.5 ± 15.3	48.9 ± 15.2	53.6 ± 14.8	0.0158
MPAP (mmHg)	34.8 ± 10.8	34.5 ± 10.7	37.7 ± 10.1	0.0172
DPAP (mmHg)	25.5 ± 9.3	25.2 ± 9.3	27.6 ± 9.7	0.0411
PCWP (mmHg)	24.3 ± 9.3	24.2 ± 9.4	24.6 ± 8.3	0.6799
TPG (mmHg)	10.6 ± 5.4	10.3 ± 5.1	13 ± 6.6	0.0012
PVR (Wood units)	2.7 ± 1.5	2.6 ± 1.4	3.5 ± 2.2	0.0012
CO (l/min)	4.2 ± 1.3	4.2 ± 1.3	4.1 ± 1.6	0.6310
CI (l/min/m^2)	2.3 ± 0.7	2.3 ± 0.6	2.2 ± 0.9	0.6422
BSA (m^2)	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	0.7217
LVEF (%)	17.2 ± 9.3	17.2 ± 9.2	16.4 ± 9.0	0.5187
LVEDD (mm)	55.4 ± 32.3	55.7 ± 32.5	53.0 ± 32.4	0.5979

SPAP, systolic pulmonary artery pressure; MPAP, mean pulmonary artery pressure; DPAP, diastolic pulmonary artery pressure; PCWP, mean pulmonary artery wedge pressure; TPG, transpulmonary gradient; PVR, pulmonary artery resistance; CO, cardiac output; CI, cardiac index; BSA, body surface area; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter.

The multivariate analysis in the hazard function showed that the variables PVR and TPG provided significant and independent contributions to the prediction of early death after cardiac transplantation (PVR: estimated coefficient = 0.791, SE = 0.0714, $P = 0.001$; TPG: estimated coefficient = 0.932, SE = 0.0217, $P = 0.0012$).

Of the 718 transplant recipients, data regarding preoperative hemodynamic support and clinical status were available in 695 patients. About 373 patients were hemodynamically stable at home, 194 were stable in hospital, 107 patients required intravenous inotropic support to remain hemodynamically stable and 21 patients required mechanical assistance with intra-aortic balloon counterpulsation or with a left ventricular assist device while awaiting cardiac transplantation. Figure 3 depicts the influence of clinical status and hemodynamic support on 30-day mortality after transplantation. Among 373 patients waiting for transplantation at home 27 (7.2%) died within 30 days postoperatively. Patients waiting in hospital and those who required intravenous inotropic support had comparable short-term mortality rates (11.3% vs. 12.1%). In contrast, among the 21 patients required mechanical support 19% died within 1 month postoperatively.

Long-term survival data were analyzed with standard Kaplan–Meier actuarial techniques for estimation of survival probabilities. For the overall group of patients, the 12-months survival was 82.8%, the 60-months survival 74.4% and the 120-months survival 56.3%. Actual survival curves according to each group of different measure of pulmonary hypertension are shown in Fig. 4. The probabilities of death at 12, 60 and 120 months after orthotopic heart transplantation were calculated in each group (Table 4). It is apparent that there was no difference in overall survival between groups A and D, in contrast to 30-day mortality.

Discussion

Right heart failure remains a substantial source of perioperative mortality for recipients after heart transplantation. The results of our study confirm the previous observation

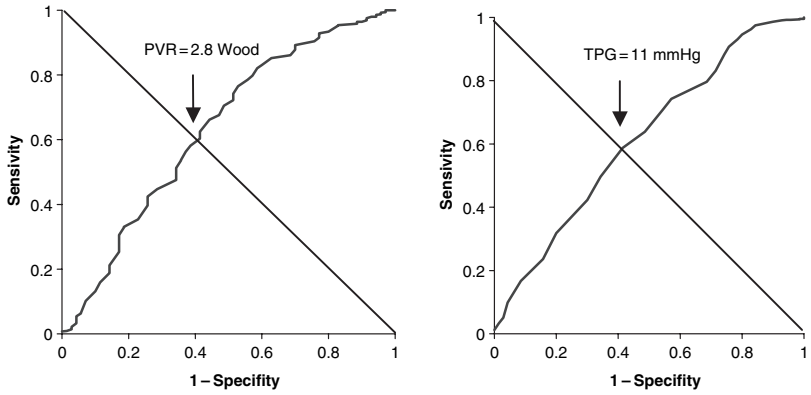

Figure 1 Estimation of risk for early mortality comparing receiver operating curves [cutoff for pulmonary vascular resistance (PVR) = 2.8 Wood units and transpulmonary pressure gradient (TPG) = 11 mmHg].

Table 3. Patients divided in preoperative hemodynamic groups.

Hemodynamic subset	Number of patients	Mortality (%)
Group A: TPG < 11 and PVR < 2.8	354	6.78
Group B: TPG < 11 and PVR > 2.8	56	8.93
Group C: TPG > 11 and PVR < 2.8	50	6
Group D: TPG > 11 and PVR > 2.8	258	14.73

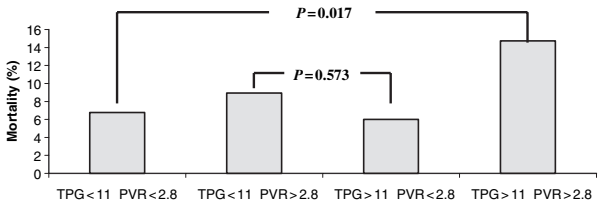

Figure 2 Patients grouped into four hemodynamic subsets comparing early death after cardiac transplantation.

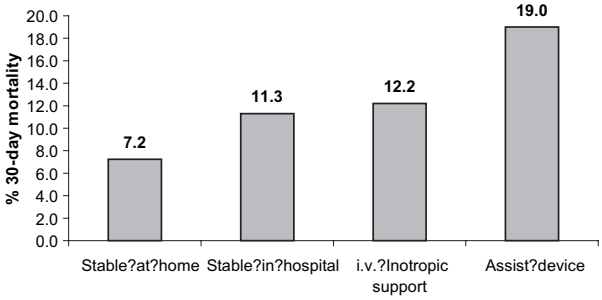

Figure 3 Influence of preoperative hemodynamic support on 30 day survival.

that early death after cardiac transplantation is significantly higher in patients with severe preoperative pulmonary hypertension [4–7]. In most centers, the clinical measure of

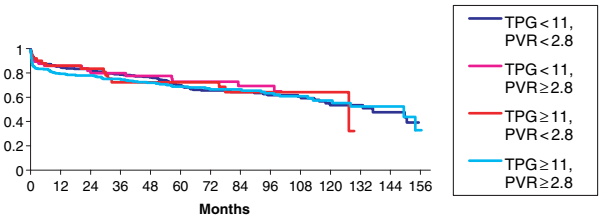

Figure 4 Long-term survival for patients after cardiac transplantation with different hemodynamic subsets (Kaplan–Meier analysis, P = NS).

preoperative pulmonary hypertension is provided by the PVR, which is used to identify patients at high risk of developing right-sided heart failure. In our series, the PVR and the transpulmonary gradient both predicted survival in the early postoperative period. Patients with hemodynamic subsets TPG > 11 mmHg and PVR > 2.8 Wood units had an approximately twofold higher risk of dying within 30 days compared to patients with TPG < 11 mmHg and PVR < 2.8 mmHg. The mortality rates in patients with TPG >11 mmHg and PVR < 2.8 Wood units or TPG < 11 mmHg and PVR > 2.8 Wood units were comparable. Therefore, we conclude that the combination of the preoperative levels of TPG and PVR is a more reliable predictor of early post-transplant survival than PVR alone.

Elevated PVR is a well-known risk factor for right ventricular failure after orthotopic cardiac transplantation. Calculated PVR has been used as a measure of impedance to right ventricular ejection, but there is no uniform agreement among the transplant centers whether the PVR is the best variable to characterize the severity of pulmonary hypertension. The experience of Costard-Jäckle *et al.* [7] revealed that patients with PVR > 2.5 Wood units and TPG > 15 mmHg have a twofold higher risk of dying within 3 months compared to patients with PVR < 2.5 Wood units and TPG ≤ 15 mmHg.

Table 4. Survival at 12, 60 and 120 months after transplantation.

	Entire cohort (%, $n = 718$)	Group A (%, $n = 354$)	Group B (%, $n = 56$)	Group C (%, $n = 50$)	Group D (%, $n = 258$)
12 months	82.8	84.6	85.7	85.9	79.2
60 months	74.4	69.8	72.7	72.2	68.7
120 months	56.3	53.5	64.9	64.2	57.2

Tenderich *et al.* [6] evaluated the PVR from 400 transplant patients over a period of 3.5 years. He came to the conclusion that the elevated PVR does not predict a bad outcome after orthotopic heart transplantation in early and late mortality. The Pittsburgh Group [8] evaluated the influence of preoperative TPG and PVR on early post-transplant mortality in 425 orthotopic transplant recipients. They found a closer correlation between the transpulmonary gradient (TPG) and early mortality than with PVR. Interestingly, they evaluated a significant difference in patients with TPG > 12 mmHg and PVR < 5 Wood units comparing to the group with TPG < 12 mmHg and PVR < 5 Wood units. Therefore, they recommend that the level of TPG should also be considered during evaluation of congestive heart failure patients for cardiac transplantation.

The ROC curves are used to determine the threshold values of patients with different outcome to distinguish the different patient groups more precisely. The ROC curves describe the relationship between sensitivity and specificity in predicting early postoperative death calculated by either TPG or PVR. To compare the overall discriminative accuracy of TPG or PVR the area under the ROC curve was measured [3,9].

The ROC curves describe graphically the relationship between the true- and false-positive rates. It is therefore an excellent method to determine the discriminative accuracy of a test measured on a continuous scale. The threshold points used to define different risk strata for associated mortality are represented as cutoff between the ROC curve and diagonal line at maximum specificity and sensitivity. These points revealed 2.8 Wood units for PVR and 11 mmHg for TPG.

Thus, this method avoids the use of arbitrarily values as were used in the past [10,11]. The more powerful specificity/sensitivity ratio of the TPG value in ROC curves comparing PVR can be explained by the independence of CO. TPG is therefore a flow-independent variable, whereas PVR is derived from TPG and CO and is dependent on flow [12].

The contour plot represents the probability for perioperative mortality depending on TPG and PVR by means of contour lines. The probabilities were modeled in a nonlinear manner using local quadratic regression. The highest probability of death within 30 days may be found in the right upper corner and the lowest probability in the lower left corner with low values of TPG and PVR, respectively (Fig. 5).

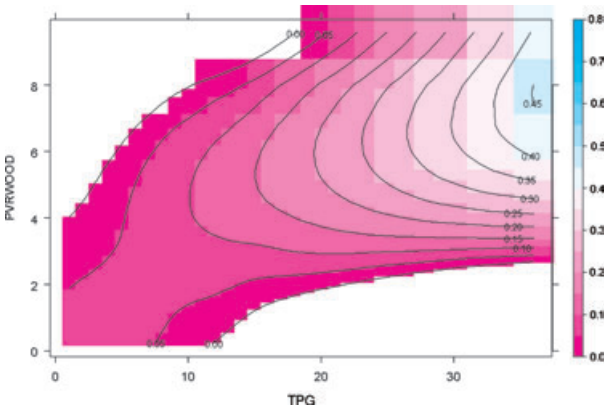

Figure 5 Probability of 30-day mortality depending on transpulmonary pressure gradient (TPG) and pulmonary vascular resistance (PVR) by means of contour lines.

In contrast to the results of Murali *et al.* [8] we did not find a significant difference between the early post-transplant mortality rates when comparing the recipient's sex. There was no difference in the prevalence of severe preoperative pulmonary hypertension in men and women (PVR > 2.8 Wood units: men 45.6%, women 48.7%, $P = 0.68$; TPG > 11 mmHg: men 48.2%, women 48.7%, $P = 0.93$).

The prognosis of patients requiring intravenous hemodynamic support or mechanical assistance was worse compared with patients who awaited cardiac transplantation at home. The worsened prognosis in the early postoperative period was expected in these high-risk patients. The literature provides contradictory data regarding the short-term outcome in patients with more or less severe hemodynamic compromise prior to transplantation. The experience of Stevenson *et al.* [11] and Costard-Jäckle *et al.* [7] is in agreement with our data, which found the 30-day mortality of patients with inotropic or mechanical support was more than doubled. Others did not find any disadvantage in terms of short-term survival between hemodynamically stable or instable patients [13,14].

The 12-month survival was 82.8% of all patients and was comparable with previous studies [12,15–17]. In

contrast to Erickson *et al.* [12] who found an increase of mortality in patients with TPG > 12 mmHg of 36% within 12 months after transplantation, in our series there was no significant difference between the groups with TPG < 11 mmHg or TPG > 11 mmHg in long-term survival.

In conclusion, data from our center identified a group of recipients, who were found to be at increased risk of early death after transplantation (PVR > 2.8 Wood units and TPG > 11 mmHg). The group with high PVR values and TPG values below 11 mmHg had the same statistically significant risk for mortality as the group with PVR values below 2.8 Wood units and TPG above 11 mmHg. Therefore, we recommend the evaluation of the pulmonary artery resistance together with the transpulmonary gradient to estimate early death after orthotopic heart transplantation. Interestingly, the long-term survival was not been affected by different values of preoperative hemodynamic measurements.

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