Regression of “fixed” pulmonary vascular resistance in heart transplant candidates after unloading with ventricular assist devices

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Pulmonary hypertension is a risk factor for early and late mortality after heart transplantation. An increase in pulmonary artery pressure secondary to long-standing elevations in left atrial pressures is observed in 33% to 72% of all patients with end-stage heart failure. This increase is disproportionate to the increase in left atrial pressure, thus causing an increased transpulmonary gradient and an increased pulmonary vascular resistance (pulmonary vascular resistance [Wood units] = transpulmonary gradient/cardiac output) over time. All patients with increased pulmonary vascular resistance greater than 3 Wood units or transpulmonary gradients greater than 10 mm Hg are subjected to a standardized protocol testing the reversibility of the elevated pulmonary artery pressure by pharmacologic interventions before cardiac transplantation. Pulmonary vascular resistance that cannot be lowered pharmacologically is termed “fixed” pulmonary vascular resistance. It has been shown that ventricular assist devices are able to reduce pulmonary vascular resistance even in patients who are unresponsive to pharmacologic reduction of pulmonary vascular resistance, thus allowing a listing for transplantation after a relatively short period of mechanical support (ie, 3–6 months).

SIGNIFICANCE OF PULMONARY HYPERTENSION IN PATIENTS WITH END-STAGE HEART FAILURE

Pulmonary hypertension (PHT) is a risk factor for early and late mortality after heart transplantation (HTX) with mortality rates up to 40%.^{1,2} Moreover, Erickson and associates² stated that right ventricular dysfunction accounts for approximately 50% of all cardiac complications and 20% of early mortality after HTX.

In the initial phase of heart failure, increases in pulmonary artery pressure (PAP) occur in proportion to an increase of left atrial pressures that can be determined indirectly by measuring the pulmonary capillary wedge pressure (PCWP). Therefore, in this early stage with initially normal pulmonary vascular resistance (PVR), no elevated transpulmonary

gradient (TPG) exists ($TPG = \text{mean PAP} - \text{PCWP}$).³ Often PVR is also described in Wood units ($WU = TPG/\text{cardiac output}$).

However, long-standing elevations in left atrial pressures result in an increase in PAP in about 33% to 72% of all patients with end-stage heart failure.^{3,4} This increase in PAP is disproportionate to the increase in left atrial pressure (PCWP), thus causing an increased TPG and an increased PVR over time. It may be speculated that the increased incidence of patients with higher PVR evaluated for HTX may be related to the fact that patients can be supported longer with modern medical treatment until they finally need to be listed for HTX.

According to the severity of PHT, 3 groups have been defined: no PHT ($PVR < 3 \text{ WU}$, $TPG < 10 \text{ mm Hg}$); mild-to-moderate PHT ($PVR 3\text{--}6 \text{ WU}$, $TPG 10\text{--}20 \text{ mm Hg}$); and severe PHT ($PVR > 6 \text{ WU}$, $TPG > 20 \text{ mm Hg}$).

All patients with increased PVR greater than 3 WU or TPG greater than 10 mm Hg are subjected to a standardized protocol testing the reversibility of the elevated PAP by pharmacologic interventions before HTX (Table 1). Pharmacologic agents tested include oxygen, nitroglycerin, sodium nitroprusside, inhaled nitric oxide, phosphodiesterase inhibitors, urapidil, prostaglandins E_1 and I_1 , and sildenafil.

PHT AND HTX

Mortality after HTX is increased if pharmacologic interventions are not able to reduce PVR below certain levels. This threshold is reported to be between 2.5 and 3.5 WU or more.^{5,6} A PVR that cannot be reduced by pharmacologic interventions below either 2.5 or 3.5 WU is usually termed “fixed” PVR. The pathophysiology of “fixed” PHT is multifactorial and seems to include vascular remodeling at the capillary level, in situ thrombosis, and vasoconstriction.⁷

The International Society of Heart and Lung Transplantation Guidelines and the Canadian Cardiovascular Society Consensus Conference on Cardiac Transplantation suggest that PAP greater than 50 mm Hg systolic, PVR greater than 4 to 5 WU, and a TPG greater than 15 to 16 mm Hg are at least relative, if not absolute, contraindications to cardiac transplantation.^{8,9} However up to date, there is no reliable hemodynamic threshold known beyond which right ventricular failure after transplant is certain to occur, nor are there values below which right ventricular failure is always avoidable.¹⁰ Even if PVR can be reduced to less than 2.5 WU by using a vasodilator and systolic blood

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pressure is less than 85 mm Hg, the patient remains at high risk for right heart failure.⁸

We have evaluated our own recent 140 HTX patients and found in 29% (40/140 patients) a PVR greater than 2.5 WU and in 5% (7/140) a PVR greater than 3.5 WU despite pharmacologic interventions (Table 1). A similar percentage of patients with fixed PVR (18%) was reported by others.⁶ In one third of patients in another series, elevated PAP was refractory to medical treatment.¹¹

Previous treatment options for patients with end-stage heart failure and fixed PVR were heterotopic HTX, combined heart-lung transplantation, and right ventricle-sparing transplantation.⁴ Inasmuch as the results of these alternative treatment options were clearly inferior to orthotopic HTX, most of these patients received no transplantation at all. Transplantation using hearts from donors with primary PHT for recipients with a high PVR (domino procedure) is another viable but rare option in transplant centers where patients undergo heart and lung transplantation for primary PHT.¹²

THERAPY WITH A VENTRICULAR ASSIST DEVICE CAN REVERSE “FIXED” PHT

As an alternative, reports and case studies have been published showing that pulsatile ventricular assist devices (VADs) reduce PHT in patients with end-stage heart failure. In 1991 Gallagher and colleagues¹³ demonstrated in 16 patients that mechanical support with a Novacor device (Novacor, Inc, Rueil-Malmaison, France) resulted in reduced PHT. This observation was confirmed by other authors in the following years.¹⁴⁻¹⁶

In the year 2000 we have started to implant left ventricular assist devices (LVAD) in patients with fixed PVR for destination therapy. A significant reduction in PVR was observed

TABLE 1. Pharmacologic testing for reversal of pulmonary vascular resistance before listing for heart transplantation: Freiburg protocol

1. Determination of baseline hemodynamics	
2. Application of oxygen	Lifeline mask 5 L/min
3. Application of nitrates	30-100 μ g/min
4. Application of inhalative iloprost	2.5-5 μ g
5. Application of dobutamine	2-6 μ g/kg/min
6. Application of inhalative nitric oxide	40 ppm or oral application of sildenafil 25 mg

after several months of mechanical circulatory support. Eventually, the patients could be listed for HTX and underwent successful transplantation. After fixed PVR was successfully reversed with pulsatile and nonpulsatile VADs in the first 6 patients, this experience was published as a preliminary report in 2004.¹⁷ The reduction in PVR occurred even in patients with markedly elevated PVR (>7 WU).¹⁷ Importantly, PHT did not return after HTX in our patients.

This observation that unloading of the left ventricle by pulsatile and nonpulsatile VADs is able to reverse previously “fixed” PVR was subsequently confirmed by other groups.^{3,6,18-21} Survival of these patients after transplantation was comparable with that of patients without prior PHT.²²

Reversal of fixed PVR occurs after a short period (weeks to months) of mechanical circulatory support. Salzberg and coworkers²¹ reported this decrease to occur after 6 weeks of LVAD support. This is confirmed by Etz and colleagues³ for the majority of their patients after implantation of nonpulsatile LVADs; after 6 months all their patients had PVR less than 3 WU. Zimpfer and associates⁶ also reported that the decrease in PVR occurred within a 6-week follow-up period.

Normalization of PVR after lowering the pressures in the left-sided heart chambers is not a recent observation in VAD

FIGURE 1. Long-term survival after heart transplantation in patients with and without prior mechanical circulatory support: Freiburg experience. VAD, Ventricular assist device.

patients with congestive heart failure. There are also reports showing the same regression of PVR after successful orthotopic HTX in patients with elevated (reversible) PVR before HTX (normalization of PVR at 1 year after HTX).¹¹ In addition, it has been known for decades that high PVR owing to severe mitral stenosis can also be reversed if pressures in the left atrium are decreased by mitral valve surgery.²³

The pathophysiology of PHT in patients with terminal heart failure is a multifactorial process not finally elucidated, but mainly related to left ventricular failure.²⁴ The mechanisms by which unloading of the left ventricle and atria (eg, by VAD) result in reversal of “fixed” PVR are unknown at present. One mechanism might be that relieved pulmonary congestion and normalized pulmonary hemodynamics reduce overproduction of intrinsic vasoconstrictors, which has been triggered by shear stress previously.³

Our own experience with mechanical circulatory support before HTX shows that the posttransplant survival is at least as good as (if not better than) that of patients receiving HTX without prior VAD support (Figure 1). These excellent long-term HTX results in patients with prior LVAD therapy as compared with those without prior LVAD support have also been reported by others.⁵

The major disadvantage of mechanical circulatory support is still the morbidity and mortality rate. However, recent publications have shown a significant improvement in the results after long-term mechanical support with 6- and 12-month survivals of 80% and 70%, respectively.²⁵

CONCLUSIONS

In conclusion, “fixed” PHT in patients with terminal heart failure can be reversed by temporary VAD support. This reduction in PVR occurs by 6 to 12 weeks in most patients, even in those with markedly elevated PVR (>7 WU). Long-term post-HTX outcome after reversal of “fixed” PHT with VADs is as good as (or even better than) that of HTX in patients without fixed PVR. However, VAD complications (morbidity and mortality) also have to be considered if this kind of treatment is chosen.

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