

# Is Severe Pulmonary Hypertension a Contraindication for Orthotopic Heart Transplantation? Not Any More

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## Summary

Pulmonary hypertension (PH) unresponsive to pharmacological intervention is considered a contraindication for orthotopic heart transplantation (OHTX) due to risk of postoperative right-heart failure. In this prospective study, we describe our experience with a treatment strategy of improving severe PH in heart transplant candidates by means of ventricular assist device (VAD) implantation and subsequent OHTX. In 11 heart transplantation candidates with severe PH unresponsive to pharmacological intervention we implanted VAD with the aim of achieving PH to values acceptable for OHTX. In all patients we observed significant drop in pulmonary pressures, PVR and TPG ( $p < 0.001$  for all) 3 months after VAD implantation to values sufficient to allow OHTX. Seven patients underwent transplantation (mean duration of support 216 days) while none of patients suffered right-side heart failure in postoperative period. Two patients died after transplantation and five patients are living in very good condition with a mean duration of 286 days after OHTX. In our opinion, severe PH is not a contraindication for orthotopic heart transplantation any more.

## Key words

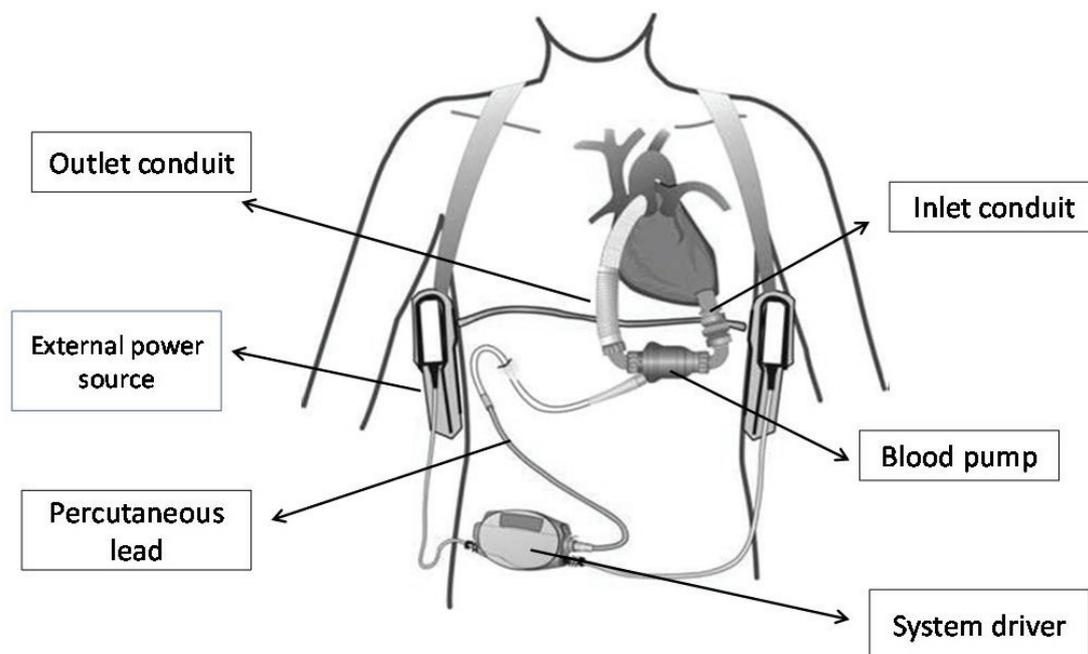
Pulmonary hypertension • Hemodynamics • Heart transplant candidacy • Ventricular assist devices

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## Introduction

Pulmonary hypertension (PH) occurs in up to 70 % of patients with moderate-to-advanced heart failure (Butler *et al.* 1999). The presence of elevated pulmonary vascular resistance (PVR) or increased transpulmonary gradient (TPG) in heart failure patients who are candidates for orthotopic heart transplantation (OHTX) represents a major risk factor for post transplant right ventricular failure and is predictive of adverse outcomes after transplantation (Chen *et al.* 1997, Tenderich *et al.* 1998). Murali and colleagues documented in patients with a TPG greater than 15 mmHg an short-term transplant mortality rate (0 to 2 days) 3 times higher than in patients with TPG <15 mmHg (Murali *et al.* 1993). Severe PH – that is, a pulmonary artery systolic pressure greater than 50 mmHg, PVR greater than 3-4 WU and TPG greater than 15 mmHg, measured after pharmacological testing – should be considered a contraindication of OHTX (Ross *et al.* 2003). Experiences with ventricular assist devices (VAD) showed a continuous reduction of PVR during mechanical circulatory support in patients with terminal heart failure. Some case reports and small studies demonstrated a significant decrease of PVR and pulmonary artery pressures during VAD support in candidates with severe PH to acceptable values for indication of OHTX (Al Khaldi *et al.* 2004, Martin *et al.* 2004, Salzberg *et al.* 2005). Learning from this experience, in 2007 we changed our strategy for heart



**Fig 1.** Heart Mate II – left ventricular assist device (LVAD), an axial-flow rotary ventricular assist device composed of a blood pump, percutaneous lead, external power source, and system driver. It is attached between the apex of the left ventricle and the ascending aorta.

transplant candidates with severe pulmonary hypertension. If a pharmacological test fails to lower PVR to less than 2.5 WU and TPG less than 15 mmHg, the patients are treated with an implantable VAD as a bridge to heart transplantation. The purpose of our prospective study was (1) to evaluate whether VAD support leads to a significant decrease or normalization pulmonary artery pressures, TPG and PVR in all patients with severe PH secondary to chronic heart failure and (2) to assess the effect of this approach on survival after OHTX in patients with pre-existing severe PH, refractory to medical therapy.

## Materials and Methods

### Patient population

Between January 2007 and October 2010, 62 patients at our clinic underwent implantation of VAD as bridge to heart transplantation [14 patients – biventricular VAD (BVAD); 48 patients – left VAD (LVAD)]. Eleven (18 %) of these patients with terminal heart failure had severe PH unresponsive to pharmacological interventions and were contraindicated to OHTX. All these patients were chosen for implantation of VAD because of an indication of pharmacological refractory PH as a bridge to candidacy. The study was approved by the institutional review board, and written

informed consent was obtained from all subjects before VAD implantation and subsequent heart transplantation.

### Devices

The first three patients were indicated for implantation of BVAD – Thoratec PVAD (Thoratec Corp., Pleasanton, CA, USA) and the next 8 patients were treated with an implantable LVAD Heart Mate II (Thoratec Corp., Pleasanton, CA, USA; Fig. 1). The technical details and implantation procedures of these devices have been described previously (Kettner *et al.* 2005, Griffith *et al.* 2001, Netuka *et al.* 2008).

### Measurement and testing reversibility of pulmonary hypertension

Right-sided heart catheterization was performed via right internal jugular vein with 7F balloon-tipped pulmonary artery (PA) catheter (Corodyn, Braun AG, Germany). The catheter position was optimized under fluoroscopic guidance. All patients were normoxemic (oxygen saturation >90 % by pulse oxymetry) at room air temperature. Cardiac output was measured by thermodilution and at least three random measurements were averaged. The PVR was calculated as mean transpulmonary pressure gradient/cardiac output. Patients with a PVR of more than 3 WU and/or a TPG of more than 15 mmHg at baseline received a continuous infusion

of PGE1 in increasing doses (alprostadil-Alprostan, Leciva, Czech Republic,) into the central vein according to our standard protocol (Kakac *et al.* 1996). In the case of persisting PH with the values for contraindication of OHTX, we indicated these patients for implantation of VAD. Three months after VAD implantation, we performed in all patients control right-sided heart catheterization, control transthoracic echocardiography and blood sampling for measurement of B-type natriuretic peptide (BNP) by CMIA (Architect BNP, Abbott, Abbott Park, Illinois).

#### Statistical analysis

The study was analyzed with the Statistical Package for the Social Sciences (SPSS Inc, Chicago, Illinois, USA). Data are presented as mean  $\pm$  SD. Paired variables were analysed by paired Student's t-test and BNP were compared using the Wilcoxon signed-rank test.

**Table 1.** Patients characteristics of the entire cohort (n=11).

Age (years)	48.9 $\pm$ 11 (range 29 - 59)
Gender	8M / 3F (73 % M)
BMI (kg/m <sup>2</sup> )	24.2 $\pm$ 4.6 (range 19.4 - 32.6)
NYHA class	III+/IV
Indications for OHTX	Cardiomyopathy ischemic 7 Cardiomyopathy dilated 3 Congenital heart disease 1
History of heart failure (years)	8.82 $\pm$ 4 (range 2 - 14)
BNP values before VAD implantation (median; ng/l)	2146
Drugs before VAD implantation (%)	Diuretics (100) Beta-blockers (82) ACE-inhibitor (73) Inotropics (36)
CRT/ICD before implantation (%)	64

BNP: B-type natriuretic peptide; BMI: body mass index; CRT: cardiac resynchronization therapy; ICD: implantable cardioverter defibrillator; OHTX: orthotopic heart transplantation; VAD: ventricular assist device

## Results

The baseline characteristics of these study patients are shown in Table 1. The mean overall age was 48.9 years (73 % were male) and mean overall body mass index was 24.2 kg/m<sup>2</sup>. All patients received maximum standard heart failure therapy. In 36 % of the patients we used small doses of dopamine or dobutamine and did not need mechanical support. The most common cause of heart failure was ischemic cardiomyopathy present in 7 patients (64 %), idiopathic cardiomyopathy was present in 3 patients (27 %). All patients had a long history of end-stage heart failure (mean 8.82 years) and PH not responsive to pharmacological intervention with PVR 6.1 $\pm$ 1.4 WU, pulmonary artery systolic pressure (PAsyst) 79.8 $\pm$ 10.7 mmHg, pulmonary artery mean pressure (PAm<sub>ean</sub>) 50.7 $\pm$ 6.5 mmHg and TPG 21.0 $\pm$ 5.2 mmHg. Detailed hemodynamic data are shown in Table 2. VAD implantation was successful in all 11 patients without complications. None of the patients required mechanical right-sided heart support after LVAD implantation. During the entire VAD support period, these patients were removed from the heart transplantation list. Overall mechanical support time was 215 $\pm$ 131 days (mean $\pm$ SD; range 119-542 days). All patients with implantable LVAD Heart Mate II were discharged from hospital after 20-60 days with standard heart failure therapy. They were trained in the routine care and handling of the assist system. Hemodynamic parameters from right-sided heart catheterization before VAD implantation, after pharmacological testing and 3 months after VAD implantation are summarized in the Table 2. In all patients we observed: a significant drop in of pulmonary pressures (PAsyst before VAD 79.8 $\pm$ 10.7 mmHg vs. after VAD 36.2 $\pm$ 7.7 mmHg; p<0.001; PAm<sub>ean</sub> before VAD 50.7 $\pm$ 6.5 mmHg vs. after VAD 21.9 $\pm$ 5.0 mmHg; p<0.001), PVR (before VAD 6.1 $\pm$ 1.4 WU vs. after VAD 2.59 $\pm$ 0.72 WU; p<0.001; in six patients decreased to  $\leq$ 2.5 WU) and TPG (before VAD 21 $\pm$ 5.2 mmHg vs. after VAD 10.5 $\pm$ 2.3 mmHg; p<0.001; 8 patients decreased to  $\leq$ 12 mmHg) 3 months after VAD implantation to values sufficient for heart transplantation (Fig. 2). Echocardiography data were obtained in all patients before and after VAD implantation and showed significant decrease of left ventricular end-diastolic dimension (LVEDD before VAD 75.5 $\pm$ 6.1 mm vs. after VAD 63.5 $\pm$ 6.2 mmHg; p<0.001) with no significant changes of the ejection fraction of the left ventricle and right ventricular dimension (Table 3). BNP values

**Table 2.** Data from right-sided heart catheterization (n=11).

Variable	Before VAD	After VAD	p value	After testing	p value
RA [mmHg]	9.7±4.9	7.2±4.7	0.026	–	–
PAsyst [mmHg]	79.8±10.7	36.2±7.7	<0.001	75.4±8.6	0.010
PAmean [mmHg]	50.7±6.5	21.9±5.0	<0.001	46.8±3.2	0.012
PWP [mmHg]	29.4±6.3	10.6±5.7	<0.001	27.3±4.6	0.729
TPG [mmHg]	21±5.2	10.5±2.3	<0.001	19.4±3.9	0.081
CO [l/min]	3.53±0.64	4.46±0.87	0.002	4.55±0.79	0.017
PVR [WU]	6.1±1.4	2.59±0.72	<0.001	4.26±0.97	0.004

CO: cardiac output; PAmean: mean pulmonary artery pressure; PAsyst: systolic pulmonary artery pressure; PVR: pulmonary vascular resistance; PWP: pulmonary capillary wedge pressure; RA: right atrium; TPG: transpulmonary gradient; VAD: ventricular assist device

**Table 3.** Data from echocardiographic examination (n=11).

Variable	Before VAD	After VAD	p value
LVEDD (mm)	75.5±6.1	65.5±6.2	<0.001
LVEF (%)	19.73±4.92	23.91±1.69	0.020
RV/PLAX (mm)	29.21±4.15	29.08±3.72	0.63

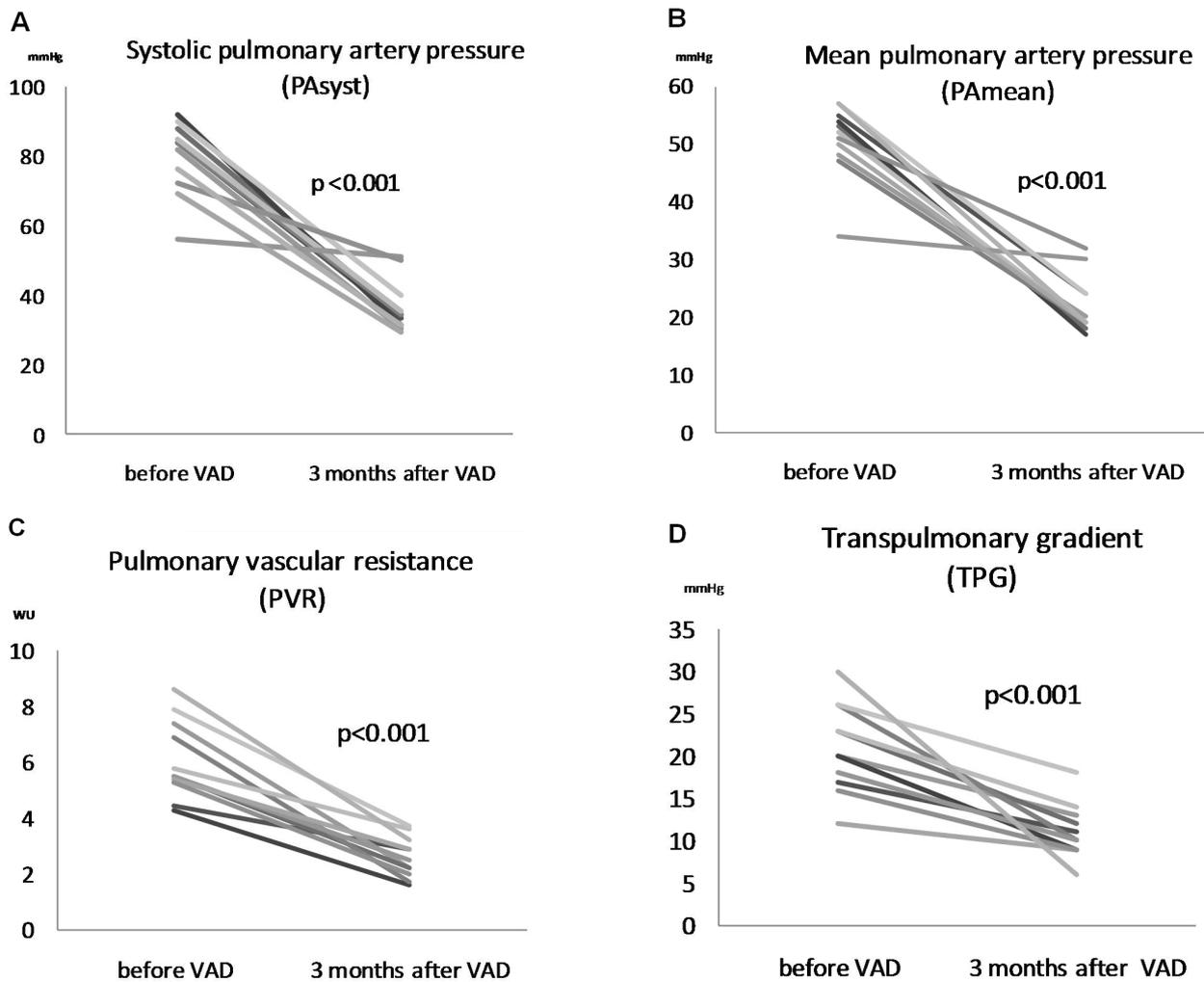
LVEDD: enddiastolic diameter of left ventricle; LVEF: ejection fraction of left ventricle; RV/PLAX: diameter of right ventricle from parasternal projection in long axis; VAD: ventricular assist device

3 months after VAD implantation significantly decreased from 2146 ng/l (median; range 382-5000) to 214 ng/l (median; range 11-880; Fig. 3). Seven patients underwent heart transplantation after a bridging period with a mean duration of 216 (range 124-542) days, 4 patients are still on waiting list of candidates for heart transplantation. Two patients died after transplantation, both due to severe bleeding and both with previously pulsatile BVAD use. None of the patients had right-side heart failure in either the perioperative or postoperative periods. Five patients are living in very good condition with a mean duration of 286 (range 87-599) days after heart transplantation. In 3 of these patients we performed right-sided heart catheterization between 11 and 21 days with a mean PVR 2.2±1.4 WU and TPG 12±8 mmHg.

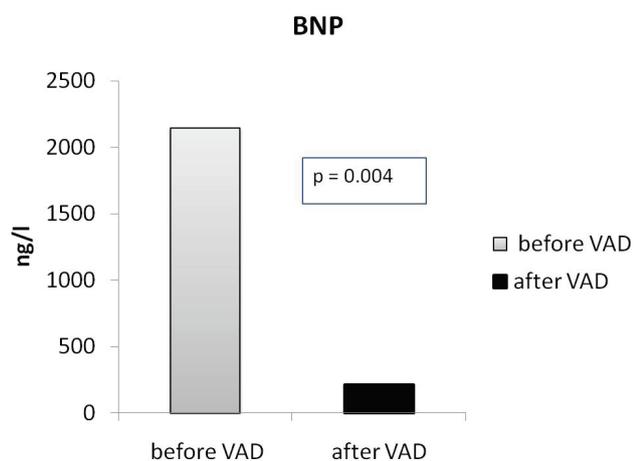
## Discussion

Pulmonary hypertension in patients with chronic heart failure is mainly due to transmission of elevated left ventricular filling pressure into pulmonary circulation. In patients with an elevated PVR it is supposed that there are changes such as dysregulation of vascular smooth muscle tone and, depending on the duration of these

processes, structural remodelling of the pulmonary vascular tree, but these mechanisms are incompletely understood. Whereas the dysregulation of the pulmonary vascular tone is readily reversed by the hemodynamic unloading or by vasodilators, structural remodelling is generally referred to as “fixed” and might be resolved, however, only slowly, taking anywhere from months to possibly years (Morales *et al.* 2000). For these reasons, the pharmacologic testing of the reversibility of PH is an essential test in the evaluation and selection of candidates for heart transplantation. Patients with pharmacological resistant PH should be considered to be a contraindication of OHTX. The cut-off values for PH as the contraindication of heart transplantation at our department are a PVR of more than 3 WU and/or a TPG of more than 15 mmHg after testing. The cut-off values are based on our long-term experience with heart transplantation. The alternative strategy for approaching OHTX in patients with severe PH is to perform heterotopic heart transplantation or heart and lung transplantation, but the survival rates are significantly lower compared to the overall survival after OHTX (Christie *et al.* 2010).



**Fig. 2.** Hemodynamic parameters before and 3 months after ventricular assist device (VAD) implantation in 11 patients: **(A)** systolic pulmonary artery pressure (PAsyst), **(B)** mean pulmonary artery pressure (PAm<sub>ean</sub>), **(C)** pulmonary vascular resistance (PVR) and **(D)** transpulmonary gradient (TPG).



**Fig. 3.** B-type natriuretic peptide (BNP) levels before and 3 months after ventricular assist device (VAD) implantation in 11 patients ( $p=0.004$ ). BNP values are expressed as median.

With increasing our experiences with implantation of VAD as bridge to transplantation, we have observed a continuous decrease in PVR during VAD support in these patients and there is growing evidence that PH in chronic heart failure can be reversed after long-term mechanical support. Accordingly, we have changed our approach to these patients. With respect to the recommendation of the International Society for Heart and Lung Transplantation (Gronda *et al.* 2006), we began to indicate patients with pharmacologically irreversible PH to BVAD implantation. In the first 3 patients of our study, we observed that 3 months after BVAD implantation a significant drop of PVR and TPG. Zimpfer and colleagues in 2007 published very good experiences with only LVAD as bridge for heart transplantation in 35 patients with PH resistant to medical treatment. In all patients from this study there was a significant decrease of PVR with values acceptable for

transplantation but more than 50 % of the patients had a severe adverse event during the period of LVAD and 11 patients died in bridging period (Zimpfer *et al.* 2007). They used 3 different types of LVADs: the DeBakey LVAD in the majority of patients, the Novacor system, and in one patient the DuraHeart system. In our remaining 8 patients (73 %) we used the small axial flow implantable pump Heart Mate II as LVAD only. In all 8 patients, we demonstrated a significant decrease of pulmonary pressures, TPG and PVR with nearly normal values and, in contrast to Zimpfer, we observed no significant complication during the study period. In accordance with reduced intracardiac pressures we demonstrated a significant fall of BNP levels after VAD implantations. Following successful heart transplantation with no right ventricle failure and favorable early values of PVR after transplantation shows that mechanical unloading leads to lasting effects on pulmonary vascular resistance. Our results support expand the existing evidence that the major component of PH due to chronic heart failure is dysregulation of vascular smooth muscle tone that results in impaired nitric oxide availability and increased endothelin expression and pulmonary vasoconstriction (Moraes *et al.* 2000). Other additional factors include hypoxia and changes in the expression of von Willebrand factor that results in the development of platelet fibrin microthrombi (Zimpfer *et al.* 2007). The true structural remodelling, which irreversible fixed of PH, is in these cases probably rare.

The major limitation of the present study is the nonrandomized design and small numbers of patients. The reason for the nonrandomized design is because severe PH is not responsive to pharmacological intervention as contraindication for OHTX. Therefore, comparing heart transplantation with and without prior VAD implantation would be ethically controversial.

## Conclusions

Pulmonary hypertension that is secondary to congestive heart failure more than likely can be reversed to the values acceptable for OHTX by the use of pulsatile or axial-flow VADs in all cases. Because of axial-flow

devices, such as the Heart Mate II, which are easier to implant (due to its smaller size and with less complications than BVAD), they are potentially suitable for this carefully selected specific candidates of heart transplantation. This strategy offers new hope and a chance of long-term survival with this approach. Accordingly, LVADs should be considered in all heart transplant candidates with PH, which are contraindication for OHTX. In our opinion, severe PH is not at the present time a contraindication for orthotopic heart transplantation.

## Conflict of Interest

There is no conflict of interest.

## Acknowledgements

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## List of Abbreviations

BMI	body mass index
BNP	B-type natriuretic peptide
BVAD	biventricular ventricular assist device
CO	cardiac output
CRT	cardiac resynchronization therapy
ICD	implantable cardioverter defibrillator
LVAD	left ventricular assist device
LVEDD	left ventricular enddiastolic diameter
LVEF	left ventricular ejection fraction
OHTX	orthotopic heart transplantation
PA	pulmonary artery
PA <sub>mean</sub>	mean pulmonary artery pressure
PA <sub>syst</sub>	systolic pulmonary artery pressure
PGE1	prostaglandin E1
PH	pulmonary hypertension
PVR	pulmonary vascular resistance
PWP	pulmonary capillary wedge pressure
TPG	transpulmonary gradient
VAD	ventricular assist device
WU	Wood units

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