Humoral and Hemodynamic Responses After Left Ventricular Assist Device Implantation and Heart Transplantation

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Left ventricular assist device (LVAD) implantation and heart transplantation (HTx) are established therapeutic approaches in the treatment of end-stage heart failure. The postoperative humoral responses to the two treatments have not yet been compared. All patients were treated with inhaled nitric oxide (iNO) on weaning from cardiopulmonary bypass as they presented with pulmonary hypertension. We investigated atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), cGMP, endothelin (ET)-1, big endothelin (big ET), and hemodynamic parameters after LVAD implantation (15 patients; age 51 ± 8 years) or HTx (10 patients; age 53 ± 6 years) preoperatively, on cardiopulmonary bypass and postoperatively up to 72 hrs after cessation of iNO. Preoperatively, cardiac index (CI), pulmonary artery pressure, pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), and mean atrial pressure (MAP) were similar for both groups. Similarly, ANP, BNP, cGMP, ET-1, and big ET were comparable before surgery. Seventy-two hours after weaning from iNO, the administered epinephrine dose was higher in the HTx group ($P = 0.003$); whereas the CVP ($P = 0.04$) and pulmonary vascular resistance (PVR; $P = 0.03$) were lower. The following humoral parameters differed markedly: ANP (preoperatively: LVAD, 99 ± 123 pg/ml; HTx, 197 ± 199 pg/ml; $P = 0.14$; vs. 72 hrs after iNO: LVAD, 110 ± 106 pg/ml; HTx, >640 ± 0 pg/ml; $P = 0.003$) and cGMP (preoperatively: LVAD, 4.4 ± 5.8 pg/ml; HTx, 5.0 ± 3.0 pg/ml; $P = 0.35$; vs. 72 hrs after iNO: LVAD, 8.0 ± 10.8 pg/ml; HTx, 26.2 ± 15.8 pg/ml; $P = 0.02$). Although the hemodynamic effects of both LVAD implantation and HTx in the treatment of end-stage heart failure are comparable, except for the effects on CVP and PVR, the humoral responses with respect to ANP and cGMP were strikingly different. These effects are independent of volume status, iNO, and ETs, suggesting a physiologic response to maintain circulatory homeostasis. Exp Biol Med 231:861–864, 2006

Key words: ANP; cGMP; endothelins; left ventricular assist device; heart transplantation

Introduction

The implantation of a left ventricular assist device (LVAD) and heart transplantation (HTx) are recognized treatments in patients with end-stage heart failure. Secondary pulmonary hypertension is often the cause of perioperative right ventricular failure in both patient groups. We have previously demonstrated that inhaled nitric oxide (iNO) selectively reduces pulmonary vascular resistance (PVR) and improves right ventricular function after LVAD implantation (1). We have also shown that iNO may modulate circulating endothelin (ET)-1 and big ET plasma levels in patients with secondary pulmonary hypertension after LVAD implantation (2). We investigated humoral and hemodynamic parameters early postoperatively to compare the effects after LVAD implantation or HTx.

Materials and Methods

Fifteen patients (mean age, 51 ± 8 years) with refractory heart failure and a low cardiac output syndrome despite maximal inotropic support, necessitating bridging therapy by emergency LVAD implantation; and 10 patients (mean age, 53 ± 6 years) with stable end-stage heart failure were included in the study. All patients presented with right ventricular dysfunction at weaning from cardiopulmonary bypass, caused by secondary pulmonary hypertension, which was treated intraoperatively with iNO. The investigation was approved by the institutional ethics committee.

The pneumatic-driven pulsatile Berlin Heart LVAD (Berlin, Germany), the electromagnetic-driven pulsatile Novacor left ventricular assist system (World Heart, Oak-

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land, CA), and the continuous flow MicroMed DeBakey ventricular assist device (MicroMed, Houston, TX) were implanted in five patients each. The patients who underwent HTx were routinely treated with cyclosporine, azathioprine, and prednisone. iNO was administered with a Siemens Servo 300/NO-B respirator (Siemens-Elema, Solna, Sweden) with an integrated option for nitric oxide respiration.

Postoperative weaning from iNO was initiated after hemodynamic stabilization and reduction of inotropic therapy by stepwise lowering of the iNO dose to prevent a possible rebound phenomenon (2).

Blood samples for ET-1, big ET, atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), cGMP, and urotensin II (UT II) were taken from a central-venous catheter, respectively. Plasma concentrations were measured preoperatively; postoperatively, at 24 hrs and 48 hrs during iNO therapy; and 72 hrs after cessation of iNO therapy.

Plasma levels for all humoral parameters, except for cGMP, which was measured with a commercially available radioimmunoassay kit (Immundiagnostik AG, Bensheim, Germany), were measured with a commercially available enzyme-linked immunosorbent assay kit (Immundiagnostik AG).

All calculations were performed using SAS Systems for Windows, v.8.2 (SAS Inc., Cary, NC). An analysis of variance for each parameter was performed to examine differences between time points for each group and overall. All parameters were statistically analyzed for differences between groups at each time point, using Wilcoxon rank sum and Student's t tests. Corresponding values of $P < 0.05$ were considered statistically significant.

Results

Hemodynamic Parameters. Before the operation, pulmonary artery pressures (values not shown), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), and mean atrial pressure (MAP) were similar for the two groups. The cardiac index (CI) was significantly lower in the HTx group ($P = 0.03$); however, unlike the LVAD recipients, none of the HTx patients required epinephrine infusion. There was a trend toward lower PVR values in HTx recipients ($P = 0.09$), and the PVR/systemic vascular resistance ratio was also lower ($P = 0.02$; Fig. 1; Table 1). Postoperatively, the administered epinephrine dose was significantly higher in the HTx group, whereas 72 hrs after weaning from iNO, CVP ($P = 0.04$) and PVR ($P = 0.03$) were lower. There was a trend toward a higher CI in the HTx group ($P = 0.07$; Fig. 1; Table 1).

Humoral Parameters. Of the humoral parameters, only UT II levels differed preoperatively between the two groups and were significantly lower in the HTx recipients ($P = 0.01$). ANP, BNP, cGMP, ET-1, and big ET were comparable before surgery (Table 2). During the postoperative course, the following humoral parameters differed markedly: ANP and cGMP were elevated in the HTx recipients as compared with the LVAD patients (Fig. 1; Table 2). In addition, BNP levels were higher in the HTx group 72 hrs after weaning from iNO.

Discussion

The purpose of the study was to investigate the impact of either LVAD implantation or HTx in patients with end-stage heart failure on sequential preoperative and postoperative hemodynamic and humoral parameters in conjunction with perioperative iNO therapy to treat secondary pulmonary hypertension. The postoperative hemodynamic effects of LVAD implantation and HTx in the treatment of end-stage heart failure are comparable, except for CVP and PVR, which were lower 72 hrs after cessation of iNO therapy. Baseline UT II concentrations were significantly higher in patients after LVAD implantation as compared with HTx patients. LVAD recipients are acutely decompensated patients receiving this treatment procedure under emergency conditions, as indicated, for example, by the need for epinephrine administration as circulatory support before LVAD implantation. UT II, thus, might be a marker of an acutely decompensated heart. During the follow-up, however, the humoral responses at the same time points were comparable for UT II. ET-1 and big ET responses were also similar in both groups. By contrast, cGMP and ANP were strikingly higher in HTx recipients, and BNP was also increased. It was previously shown that ANP and cGMP values are elevated after HTx (3), but a direct comparison to an alternative therapy, such as LVAD implantation, has not been reported thus far, to our knowledge. ANP is a potent pulmonary vasodilator with antiproliferative and diuretic properties. The major stimulant for ANP release is myocyte stretch in the atria. It has not been established whether atrial wall stretch liberates ANP directly, or *via* factors such as NO or ET-1 as a response to distension (4). The biologic activities of the natriuretic peptides are mediated *via* the second messenger, cGMP. It is notable that the CVP and PVR values were lower in HTx recipients as compared with LVAD patients, ruling out volume status, pulmonary hypertension, and right ventricular compromise as the cause for elevated natriuretic peptides and cGMP. Because ANP, similar to NO, activates guanylate cyclase activity, is a potent pulmonary vasodilator, and possesses additional diuretic properties, ANP and cGMP levels that were much higher may have contributed to lower CVP and PVR values in HTx patients. However, despite increased circulating natriuretic peptides, HTx patients often present with volume overload, hypertension, and renal impairment, suggesting at least a relative renal hyporesponsiveness to ANP (3).

In left ventricular failure, PVR increases, which might be attributed to dysregulation of the endothelium in the pulmonary circulation, with an impaired release of NO and an increased expression of ET (5). ET is increased in pulmonary hypertension (2), and the effects of ANP are directly antagonistic to the renin-angiotensin-aldosterone

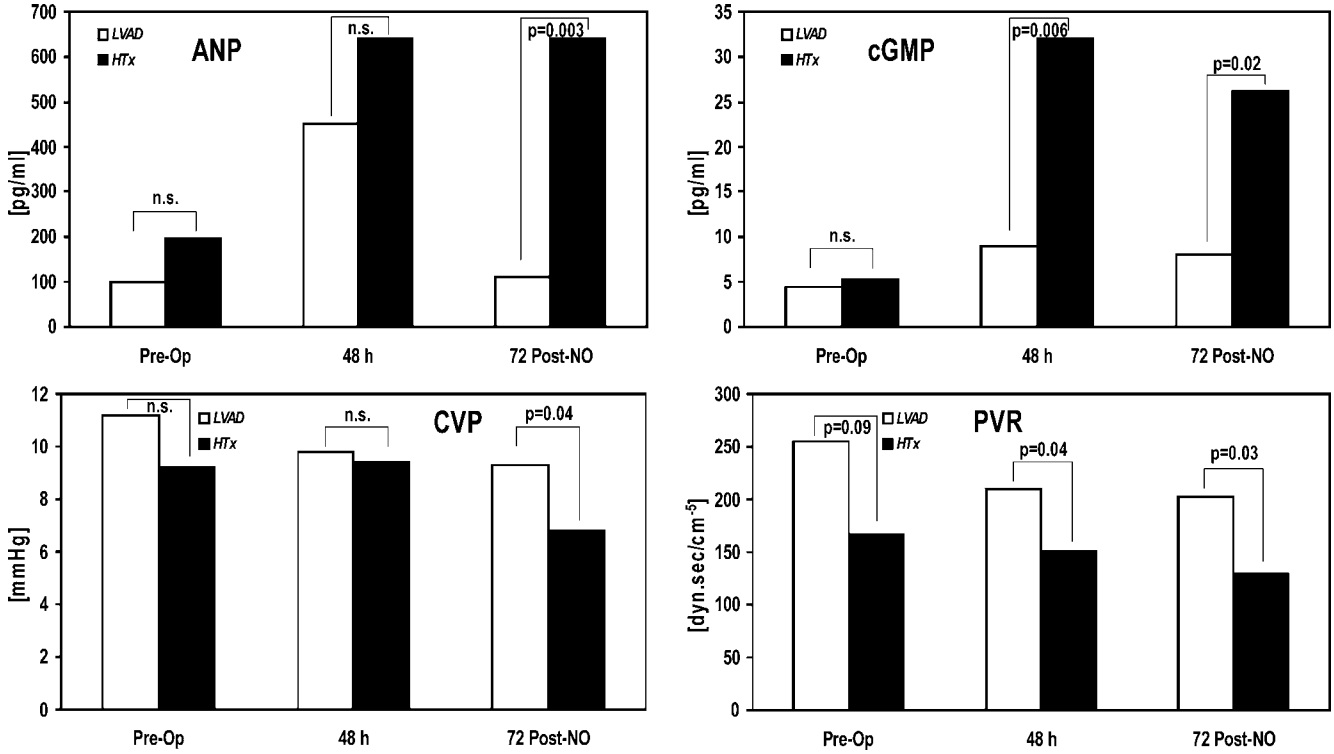

Figure 1. (Upper panel) Left, ANP; right, cGMP. (Lower panel) Left, CVP; right, PVR. Preop, preoperatively; 72 hrs post-NO, 72 hrs after cessation of iNO. Mean ± SD.

system and to ET (6). It has been suggested that ET-1 may stimulate ANP release (4). The ANP and cGMP systems are activated in severe pulmonary hypertension, and ANP levels correlate with right ventricular function as well as preload and afterload (7). The effects of iNO on circulating plasma levels of ET-1 and big ET in patients with secondary pulmonary hypertension after LVAD implantation have previously been described, and assume that iNO may decrease ET-1 and big ET release (2). However, our data indicate that ANP and cGMP plasma concentrations are independent of circulating ET levels in HTx patients. It is notable that there was no significant difference regarding the administered doses and the duration of iNO therapy between LVAD recipients and HTx patients in this investigation. Thus, a major impact of iNO therapy or ETs on natriuretic peptides and cGMP after HTx is not supported by our study.

Based on our findings, the transplanted heart itself or transplant-associated factors, such as the bicaval anastomoses influencing atrial geometry (8) or immunosuppression (9), may play a role. Elevated ANP levels found late after HTx militate against denervation as a cause (8). A relative hyporesponsiveness to ANP in HTx patients has previously been reported (3), supporting a physiologic

Table 1. Time Course of Hemodynamic Parameters and Epinephrine Dose[a]

	Preoperative		24 hrs		48 hrs		72 hrs after NO	
	LVAD	HTx	LVAD	HTx	LVAD	HTx	LVAD	HTx
MAP (mm Hg)	79 ± 13	85 ± 20	73 ± 10	85 ± 8**	78 ± 13	76 ± 11	77 ± 8	75 ± 5
CI (l/min/m^2)	2.5 ± 0.5	2.0 ± 0.1*	3.0 ± 0.5	3.4 ± 0.4	3.3 ± 0.7	3.6 ± 0.8	3.1 ± 0.5	3.7 ± 0.6
CVP (mm Hg)	11 ± 5	9 ± 3	10 ± 3	9 ± 2	10 ± 2	9 ± 2	9 ± 3	7 ± 1*
PCWP (mm Hg)	22 ± 8	17 ± 8	9 ± 5	10 ± 2	10 ± 5	11 ± 2	8 ± 4	11 ± 3
PVR (dyn·sec/cm^5)	255 ± 109	167 ± 21	94 ± 60	154 ± 46	210 ± 65	151 ± 49*	203 ± 6	129 ± 50*
PVR/SVR (dyn·sec/cm^5)	0.27	0.10*	0.23	0.16	0.26	0.19	0.22	0.16
Epinephrine (mg/min/kg)	0.07 ± 0.10	0.0	0.07 ± 0.05	0.31 ± 0.16***	0.04 ± 0.03	0.33 ± 0.29**	0.02 ± 0.03	0.10 ± 0.06**

[a] Data presented as mean ± SD; Wilcoxon rank sum test.
*$P < 0.05$; **$P < 0.01$; ***$P = 0.0001$.

Table 2. Time Course of Humoral Parameters[a]

	Preoperative		24 hrs		48 hrs		72 hrs after NO	
	LVAD	HTx	LVAD	HTx	LVAD	HTx	LVAD	HTx
ANP (pg/ml)	99 ± 123	197 ± 199	125 ± 112	640 ± 0***	451 ± 327	640 ± 0	110 ± 106	640 ± 0**
cGMP (pg/ml)	4.4 ± 5.8	5.0 ± 3.0	11.4 ± 16.4	17.9 ± 14.1	8.9 ± 12.1	32.1 ± 23.3**	8.0 ± 10.8	26.2 ± 15.8*
BNP (pg/ml)	53 ± 43	124 ± 202	111 ± 131	114 ± 76	72 ± 70	211 ± 301	124 ± 257	176 ± 114*
UT II (pg/ml)	5470 ± 3666	2068 ± 1183**	5544 ± 2730	8460 ± 1115	5753 ± 2922	5418 ± 2102	5789 ± 1635	6330 ± 5111
big ET (fmol/ml)	3.6 ± 2.7	2.0 ± 1.4	3.6 ± 1.8	3.1 ± 1.2	3.5 ± 1.3	3.3 ± 1.8	8 ± 4	11 ± 3
ET-1 (fmol/ml))	1.2 ± 0.7	0.9 ± 0.8	0.9 ± 0.7	0.7 ± 0.5	0.7 ± 0.6	0.6 ± 0.5	0.4 ± 0.3	2.1 ± 3.2

[a] Data presented as mean ± SD; Wilcoxon rank sum test.
*$P < 0.05$; **$P < 0.01$; ***$P = 0.0002$.

demand to increase natriuretic peptides after HTx. However, the exact mechanisms are not yet elucidated.

In conclusion, our study indicates that neither volume and hemodynamic status, iNO therapy, nor ET are responsible for the elevation of ANP and cGMP early after HTx as compared with LVAD recipients. As discussed, the early postoperative humoral responses with respect to ANP and cGMP may be physiologic responses to maintain circulatory homeostasis in HTx recipients.

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