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ORIGINAL ARTICLE

Neurohumoral and inflammatory markers for prediction of right ventricular failure after implantation of a left ventricular assist device

Felix Hennig, MD · Alexander V. Stepanenko, MD
Hans B. Lehmkuhl, MD · Marian Kukucka, MD
Michael Dandel, MD, PhD
Thomas Krabatsch, MD, PhD
Roland Hetzer, MD, PhD
Evgenij V. Potapov, MD, PhD

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Abstract
Purpose. Implantation of a left ventricular assist device (LVAD) is an established treatment for end-stage heart failure. Right ventricular dysfunction develops in 20%–50% of patients after device implantation, leading to prolonged hospital stays and elevated mortality rates. However, prediction of right ventricular failure remains difficult.
Methods. A total of 40 patients who received an LVAD for chronic end-stage heart failure between May 2001 and December 2002 were evaluated. The patients were divided retrospectively into two groups: group I ($n = 26$), with no apparent postoperative right ventricular failure; and group II ($n = 14$), with right ventricular failure after implantation defined by the presence of two of the following criteria during the first week after surgery: mean arterial pressure ≤55 mmHg, central venous pressure ≥16 mmHg, mixed venous saturation ≤55%, cardiac index <2 l/min/m^2, inotropic support score >20 units or an apparent need for mechanical right ventricular support. Hemodynamic, echocardiographic, neurohumoral, and inflammatory parameters were evaluated 24 h before implantation of the LVAD.
Results. Levels of procalcitonin, neopterin, n-terminal-pro-brain natriuretic peptide, and big endothelin-1 were significantly lower in group I: 0.106 vs. 0.322 ng/ml, P = 0.048; 10.5 vs. 20.7 ng/ml, P = 0.018; 6322 vs. 17174 pg/ml, P = 0.032; 1.6 vs. 19.5 pg/ml, P = 0.02, respectively. Levels of creatinine kinase and creatinine were significantly lower in group I than in group II: 24 vs. 40 U/l, P = 0.034; 1.3 vs. 2.3 mg/dl, P = 0.008, respectively.
Conclusion. Preoperative evaluation of markers of inflammation and neurohumoral activation may provide additional information for predicting right ventricular failure after implantation of an LVAD.

Key words Left ventricular assist device · Right ventricular failure · Implantation · Ventricular assist device · Brain natriuretic peptide · Inflammation · Neurohumoral

F. Hennig (✉) · A.V. Stepanenko · H.B. Lehmkuhl
M. Kukucka · M. Dandel · T. Krabatsch · R. Hetzer
E.V. Potapov
Department of Thoracic and Cardiovascular Surgery, Deutsches Herzzentrum Berlin, Augustenburger Platz 1, Berlin 13353, Germany
Tel.+49-30-4593-2063; Fax +49-30-4593-2079
e-mail: fhennig@dhzb.de

Introduction

Left ventricular assist devices (LVADs) are being used with growing success for treatment of end-stage congestive heart failure.[1–3] The survival of patients treated with LVADs in a bridge-to-transplant setting and for permanent support is significantly better than that of patients on continuous inotropic support or medical therapy.[4] Despite growing experience in patient selection and significant improvements in device technology, postoperative right ventricular failure (RVF) remains one of the main complications.[5] Especially with second- and third-generation miniaturized devices, although the perioperative incidence of bleeding and infection has markedly decreased, RVF has become a major postoperative issue. Being associated with coagulopathy, transfusion, and subsequent multi-organ failure, RVF prolongs the time in the intensive care unit (ICU) and increases

mortality.[6] Therefore, there is a need to identify preoperative predictors of RVF. In recent years, various markers of neurohumoral activation and inflammation have gained a significant role in estimating the short- and long-term prognosis of patients suffering from heart failure.

Several studies have been performed to identify clinical and hemodynamic predictors for RVF, but reliable predictors have not yet been found. We investigated neurohumoral markers and markers of inflammation as preoperative predictors of RVF after LVAD implantation.

Methods

The institutional ethics committee approved the study, and informed consent was obtained from all patients or, if they were unable to sign, from their relatives.

Between May 2001 and December 2002, a total of 40 patients suffering from inotrope-dependent end-stage congestive heart failure received an LVAD in a bridge to transplant setting. Inotrope dependency was considered to be present if the level of inotropic support was >3, calculated using a modified inotropic score.[4] Briefly, the doses of dopamine, dobutamine, and enoximone (in micrograms per kilogram body weight per minute) were added. The doses of milrinone were multiplied by 15 and then added; and the doses of epinephrine and norepinephrine were multiplied by 100 and then added.

On admission and during follow-up, transesophageal echocardiography measuring right and left ventricular ejection fractions (RVEF and LVEF, respectively) and the right and left ventricular end-diastolic diameters (RVEDD and LVEDD, respectively) was performed routinely in all patients. Every day hemodynamic parameters, including data from pulmonary catheterization, were monitored in all patients in supine position for at least 30 min. Additionally, the patients underwent clinical examination, and the medication administered was recorded. Contemporaneously, blood samples were drawn into prechilled standard serum and plasma tubes, immediately centrifuged at 4°C and 3000 rpm, and stored at −80°C. The samples were analyzed at the end of the study, after the planned number of patients were acquired.

The patients were divided retrospectively into two groups: group I ($n = 26$), with no apparent RVF after LVAD implantation; and group II ($n = 14$), with RVF after LVAD implantation. All implantations were performed without use of cardioplegic arrest. Perioperative prevention and treatment of RVF were performed as described elsewhere, including careful administration of fluids and inotropes as well as a reduction of right ventricular afterload by administration of inhaled NO, inhaled iloprost, and oral sildenafil.[7–11]

Patients were defined as suffering from RVF if in the absence of pericardial tamponade two or more of the following criteria were met during the first 48 h after LVAD implantation: mean arterial pressure <55 mmHg, central venous pressure (CVP) ≥16 mmHg, mixed venous saturation <55%, cardiac index (CI) <2 l/min/m^2, inotropic support >20 units. RVF was also assumed to be present if placement of a right ventricular assist device (RVAD) or a total artificial heart (TAH) was necessary.

Laboratory measurements

For all measurements, blood drawn 24 h prior to LVAD implantation was used. Big ET-1 was measured employing an assay commercially available from Assay Designs (catalogue no. 900-022; Ann Arbor, MI, USA). The sensitivity of the test was 0.23 pg/ml; the intraassay coefficient of variance (CV) was <5% and the interassay CV was <4%. The reference level was 2.1 pg/ml.

The amino-terminal part of N-terminal pro-brain natriuretic peptide (NT-proBNP) was measured by a commercially available Roche Diagnostics assay (Mannheim, Germany, catalogue no. 03121640). Procalcitonin and neopterin were measured using commercially available assays (B.R.A.H.M.S., Berlin, Germany).

Statistical analysis

Echocardiographic, hemodynamic, neurohumoral, and inflammatory parameters measured before LVAD implantation were analyzed. The data obtained 24 h before implantation of the assist device were compared between the two groups. Patients who initially received biventricular support were excluded from the analysis. Patients with preoperative need for extracorporeal membrane oxygenation (ECMO) or extracorporeal life support were also excluded. The statistical analysis was performed using SPSS 10.0.5 for Windows.

For quantitative data, median and quartiles or the mean and standard deviation were calculated. Qualitative data are reported as relative frequencies and percentages. Levels of the markers of inflammation and neurohumoral activation are reported as the median and quartiles. The Kruskall-Wallis, Mann-Whitney or χ^2 tests were applied to test differences between groups. $P < 0.05$ was considered statistically significant.

Results

Of the 40 patients (mean age 53.6 ± 12.7 years, range 24–77 years), 38 were men. The demographics and selected results of clinical, laboratory, and echocardiographic examination are presented in Table 1.

All patients received an LVAD (group I: 3 Novacor, 11 DeBakey, 8 Berlin Heart Excor, 4 Berlin Heart Incor I; group II: 3 Novacor, 6 DeBakey, 4 Berlin Heart Excor, 1 Berlin Heart Incor I). Additional RVAD implantation was not performed. There was no statistically significant difference in length of time on cardiopulmonary bypass (CPB) or the amount of blood products used. The incidence of RVF did not vary between pulsatile or continuous-flow devices. The 30-day survival was 81% in group I and 36% in group II.

Patients with no apparent RVF (group I) showed significantly higher systemic blood pressures than did patients with RVF (group II) (Table 1). Creatine kinase levels were significantly lower in patients in group I than in those in group II) ($P = 0.034$). Patients in group I showed significantly lower creatinine levels than did patients in group II (Table 1).

Echocardiography indicated that the patients in group I had a slightly higher right ventricular ejection fraction (RVEF) than patients in group II (Table 1). NT-proBNP levels were significantly higher in group II patients than in group I patients (17 174 vs. 6322 pg/ml; $P = 0.032$) (Fig. 1), as were the big endothelin-1 levels (19.5 vs 1.6 pg/ml; $P = 0.02$) (Fig. 2), the procalcitonin levels (0.322 vs. 0.106 mg/dl; $P = 0.048$) (Fig. 3), and the neopterin levels (20.7 vs. 10.5 mg/dl; $P = 0.018$) (Fig. 4).

Table 1 Demographic, routine laboratory, and hemodynamic parameters 24 h prior to VAD implantation

Parameter	Group I: no apparent RVF	Group II:RVF	*P**
No. of patients	26	14	
Age (years)	54.7 ± 12.3	55.4 ± 9.0	0.331
Creatine kinase (U/l)	23.9 ± 42.7	39.7 ± 37.7	0.034
Creatinine (mg/dl)	1.3 ± 0.5	2.3 ± 1.6	0.008
Bilirubin (mg/dl)	1.75 ± 0.94	2.22 ± 1.25	0.305
AST (U/l)	51 ± 134	21 ± 13	0.168
WBC (10^3/μl)	10.1 ± 4.3	11.2 ± 4.4	0.305
LVEF (%)	18 ± 5	17 ± 4	0.836
LVEDD (mm)	74 ± 8	69 ± 6	0.08
RVEF (%)	35 ± 11	28 ± 4	0.042
RVEDD (mm)	35 ± 4	37 ± 5	0.283
Cardiac index (l/min/m^2)	2.32 ± 0.73	2.60 ± 0.76	0.292
Heart rate (b/min^{-1})	96 ± 20	97 ± 23	0.944
BP (mmHg)			
Systolic	99 ± 16	91 ± 15	0.042
Diastolic	59 ± 11	51 ± 9	0.042
Mean	72 ± 12	64 ± 10	0.045
Pulmonary BP (mmHg)			
Systolic	48 ± 17	49 ± 15	1.000
Diastolic	27 ± 9	28 ± 9	0.917
Mean	36 ± 12	37 ± 11	0.780
Wedge pressure (mmHg)	22 ± 8	22 ± 8	0.890
CVP (mmHg)	11 ± 6	14 ± 7	0.235
SVR (dynes × s/cm^5)	1153 ± 530	904 ± 399	0.137
PVR (dynes × s/cm^5)	312 ± 196	252 ± 124	0.404
Mixed venous saturation (%)	60.6 ± 10.8	63.0 ± 5.7	0.813
Inotropic score	11 ± 8	22 ± 34	0.243
Time on bypass (min)	105 (59–71)	133 (56–258)	0.871
Packed RBCs (units)	2.7 (0–18)	5.1 (0–15)	0.435
FFP (units)	7.7 (0–22)	8.1 (3–18)	0.787
Platelets (units)	0.8 (0–4)	0.3 (0–1)	0.654

Data are presented as the mean ± SD

AST, aspartate aminotransferase; BP, blood pressure; CVP, central venous pressure; FFP, fresh frozen plasma; LVEDD, RVEDD, left and right ventricular end-diastolic diameter, respectively; LVEF, RVEF, left and right ventricular ejection fraction, respectively; PVR, pulmonary vascular resistance; RBCs, red blood cells; SVR, systemic vascular resistance; VAD, ventricular assist device; WBC, white blood cell count

*P was calculated using the Mann-Whitney or χ^2 test

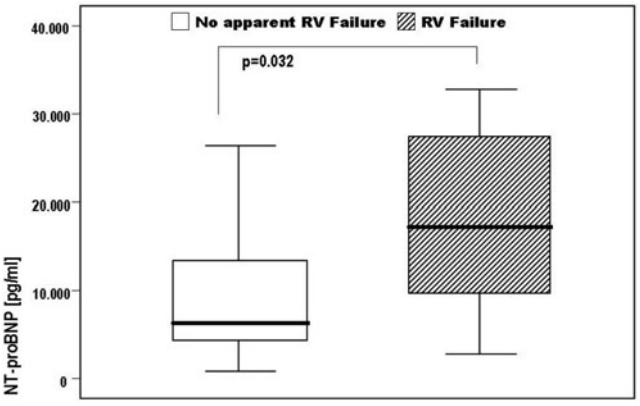

Fig. 1 Median and quartiles of levels of N-terminal pro-brain natriuretic peptide (*NT-proBNP*) in patients with normal postoperative right ventricular (*RV*) function versus those in patients with RV failure

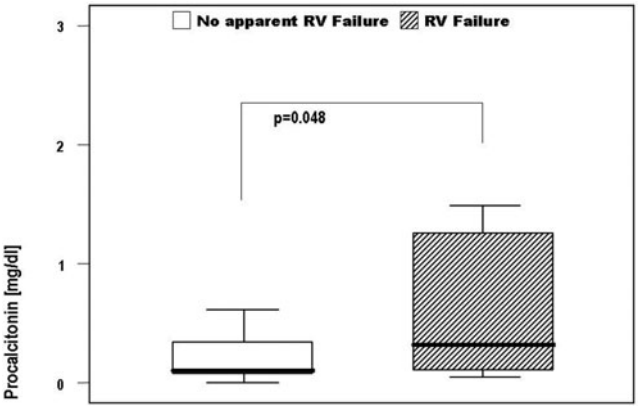

Fig. 3 Median and quartiles of levels of procalcitonin in patients with normal postoperative RV function versus those in patients with RV failure

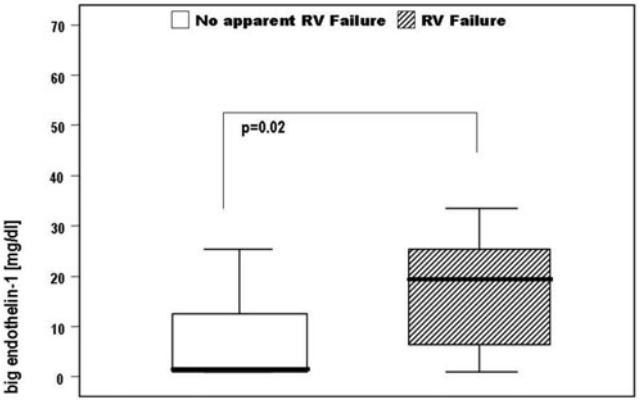

Fig. 2 Median and quartiles of levels of big endothelin-1 in patients with normal postoperative RV function versus those in patients with RV failure

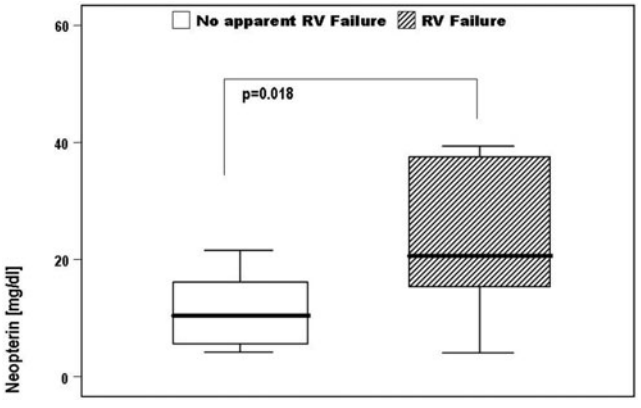

Fig. 4 Median and quartiles of levels of neopterin in patients with normal postoperative RV function versus those in patients with RV failure

Discussion

Patients with RV failure after LVAD implantation present with significantly elevated levels of neurohumoral (big endothelin-1, NT-proBNP) and inflammatory (neopterin, procalcitonin) markers preoperatively. RVF is still a major problem following LVAD placement for end-stage heart failure. It is associated with significant morbidity and mortality, even after the introduction of several sophisticated treatment strategies, including right heart bypass; administration of inhaled NO, sildenafil, and ilomedin; restricted fluid replacement and catecholamine administration; and running the pump flow at a level not higher than necessary for adequate organ perfusion.[7–11]

At present, there is no uniform definition for RVF available; and the reported incidence varies between 7% and 50% depending on the patient groups and definitions.[12,13] However, the definition used in this study has been accepted for a multicenter international U.S. Food and Drug Administration (FDA)-approved trial on the effect of inhaled NO on RVF after LVAD implantation.

There are several theories to explain the development of RVF after LVAD placement: right ventricular volume overload caused by an LVAD flow exceeding the rate necessary for optimal end-organ perfusion; changes in right ventricular geometry following unloading of the left ventricle; elevated right ventricular afterload caused by changes in the pulmonary vasculature; or faulty intraoperative cardioprotection.[14] Additionally, the release of cytokines and neurohormones may directly influence right ventricular performance or pulmonary vascular resistance and hence have predictive value.[15] From this study, it is not clear whether the preoperatively observed elevations in neurohormones and cytokines ultimately contributed to the development of RVF or indicated an

already existing higher susceptibility for RVF. To date, none of the above can independently explain the development of RVF but provided that the operative technique and postoperative management are sound, the patients' preoperative status must determine their susceptibility for postoperative RVF.

The present study supports previous findings that patients with adequate right ventricular function after surgery had significantly higher systemic blood pressure preoperatively.[16] Low pulmonary artery pressure and low right ventricular stroke work index (RVSWI) have been shown to be more prevalent in RVF patients,[6,8,17] but in our study such differences could not be found. Possibly this is caused by different criteria for defining RVF. While the need for an RVAD characterizes only the sickest patients, we focused more broadly on all clinically relevant RVF as additively characterized by the need for elevated inotropic support and hemodynamic alterations.

Patients in group I also showed lower creatinine and creatinine kinase levels than patients in group II. However, although significant, these differences are less suitable for the decision-making process because of the large ranges. It has been recognized that these parameters are an expression of beginning multi-organ failure and can provide prognostic information when viewed in the general context only.[6,18,19]

The main finding of the study was that the neurohumoral and inflammatory markers are eligible for preoperative prediction of postoperative RVF. Previous studies that focused on end-stage heart failure showed that additional prognostic information can be gained by measuring neurohumoral markers, such as natriuretic peptides and big endothelin, as well as markers of inflammation such as procalcitonin and neopterin.[20,21] A calcitonin precursor molecule, procalcitonin was first described as elevated in patients with bacterial infection. Additionally, there is evidence that it may serve as a marker for the severity of heart failure.[22] Neopterin belongs to a group of molecules associated with cell-mediated immunity and is secreted foremost by monocytes and macrophages. In patients with dilated cardiomyopathy, elevated levels indicate advanced disease and a poor prognosis.[23] NT-proBNP is a cleavage product that originates from the synthesis of BNP, a natriuretic peptide mainly produced in the ventricular myocardium of patients suffering from heart failure. Serum levels of NT-proBNP correlate with the severity of heart failure and the patient's prognosis.[24] Big endothelin-1, a precursor in the synthesis of endothelin-1, is a strong vasoconstrictor peptide and a strong independent predictor of survival in patients with severe heart failure.[25]

There is strong evidence that mechanisms of inflammation contribute to worsening of the cardiorespiratory condition of patients suffering from heart failure. In our study, patients who developed RVF showed significantly elevated markers of inflammation. Accordingly, Sharma and Anker detected chronic low-grade inflammation in patients with severe heart failure as their condition worsened.[26] Data published by Kormos and colleagues shows a significant correlation between the number of perioperative blood transfusions and the incidence of RVF, which could also point to activation of the inflammatory system.[27]

Numerous studies have evaluated the prognostic value of single and serial measurements of natriuretic peptides in patients with heart failure.[28,29] Recently, Gardner et al. demonstrated that a single measurement of NT-proBNP in patients with advanced CHF can help identify patients at highest risk of death; it is a better prognostic marker than the LVEF, peak VO_2, or the Aaronson Score alone.[30]

Although the differences between the groups were significant, the predictive value of the markers investigated was not satisfactory. Multivariate analysis did not identify additional prognostic information. However, the study encompassed only a small number of patients, and different types of LVAD were used. A prospective study with a larger patient cohort and using commercially available automated assays is necessary to support the current findings.

Conclusion

The neurohormones and markers of inflammation investigated in this study showed significant differences preoperatively that correlated with postoperative right ventricular function. Hence, these parameters should be taken into consideration when evaluating the patient for the most suitable mechanical circulatory support system i.e., LVAD vs. bilateral VAD, or a total artificial heart.

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