Neurohormonal Activation and Exercise Function in Patients With Severe Heart Failure and Patients With Left Ventricular Assist System*

A Comparative Study

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Objectives: The aim of this study was to evaluate the effects of implantation of a left ventricular assist system (LVAS) on the neurohormonal status, exercise capacity and symptomatic state in patients with severe congestive heart failure (CHF).

Background: Severe CHF is characterized by decreased exercise tolerance and activation of several neurohormonal systems.

Methods: Parameters of neurohormonal activation and exercise capacity in patients with LVAS (n=7) were compared with those in groups of New York Heart Association (NYHA) class 3 (n=121) and class 4 (n=81) patients. Plasma levels of norepinephrine (NE), plasma renin activity (PRA), and atrial natriuretic peptide (ANP) and maximal and submaximal exercise capacities were measured monthly in LVAS patients and compared with results in CHF patients.

Results: Plasma NE and PRA levels were significantly lower in LVAS patients than in NYHA class 4 patients, and plasma ANP levels in LVAS patients were significantly lower than those in NYHA class 3 and 4 patients.

Conclusion: We conclude that the LVAS lessens the neurohormonal activation and exercise intolerance characteristic of the CHF state and that the exercise capacity early after LVAS (<4 months) is similar to that observed in NYHA class 3 patients.

(CHEST 1995; 107:1499-1503)

Key words: atrial natriuretic peptide; congestive heart failure; exercise tolerance; left ventricular assist system; neurohormones; norepinephrine; plasma renin activity

Congestive heart failure (CHF) is characterized by decreased exercise tolerance and neurohormonal activation including sympathetic nervous system stimulation, activation of the renin-angiotensin-system, and increased secretion of atrial natriuretic peptide (ANP). Improvement in cardiac pump function by cardiac transplantation is associated with partial reversal of these abnormalities.¹,² The shortage of donor organs and complications of immunosuppression have led to increased interest in mechanical circulatory assistance for both the temporary support of the patient awaiting transplantation and as a permanent form of cardiac support. Although a biventricular device (totally artificial heart) has previously been utilized as a "bridge" to transplant, more recently, ventricular assist systems, particularly left ventricular, have been used.³

The typical left ventricular assist system (LVAS) candidate is a bedridden, critically ill, New York Heart Association (NYHA) class 4 CHF patient who is dependent on intravenous inotropic and, in many cases, intraaortic balloon support. The LVAS provides the potential of pretransplant rehabilitation by allowing the patient to become ambulatory, improve muscle tone and increase mass, and improve nutritional status prior to transplantation.³ Whether the abnormal neurohormonal and exercise profiles of these patients improve with implantation or still resemble those of NYHA class 4 patients has not been elucidated.

The purpose of the present study was to evaluate the neurohormonal status and exercise capacity of
CHF patients after LVAS implantation and compare the results with those in a group of NYHA class 3 and 4 CHF patients.

METHODS AND PATIENT POPULATION

The following methods were utilized in both the LVAS and CHF patients. Plasma norepinephrine (NE), renin activity (PRA), and ANP were measured by methods previously described. Submaximal exercise testing with measurement of total distance walked over 6 min was performed utilizing the methodology of Guyatt et al. Maximal exercise tolerance was assessed utilizing either the modified Naughton treadmill protocol with 2-min stages or the modified Wassermann ramp protocol using bicycle ergometry. Endpoints included total exercise time and peak oxygen consumption.

All blood samples for neurohormone measurement were obtained after at least 50 min following venous cannulation with the patient in the supine position. The samples were collected in chilled test tubes and cold centrifuged at 3,000 revolutions per minute for 15 min before being processed.

In the LVAS patients, neurohormone levels were obtained within 48 hs of the exercise test. Angiotensin-converting enzyme inhibitors were held for at least 24 h prior to neurohormonal sampling in all NYHA class 3 and 4 CHF patients, but two patients on LVAS were receiving these medications. Testing was performed monthly after LVAS implantation until heart transplantation (n=6) or death (n=1).

The point at which the patient achieved the greatest oxygen consumption during maximal exercise was utilized for reporting peak oxygen consumption, 6-min walking distance, and neurohormonal levels in the LVAS patient group.

All LVAS patients had cardiac output measured prior to placement using the thermodilution method. Cardiac output post-LVAS was calculated as the product of the stroke volume ejected from the left ventricular assist device multiplied by the pump rate.

Kruskal-Wallis one-way analysis of variance and a nonparametric multiple comparison test based on the Mann-Whitney test as described in the BMDP 3S software analysis program were used for comparing PRA values. One-way analysis of variance and Scheffe's method of pairwise comparison, as described in the BMDP 7D software analysis program, were used to compare NE, ANP, age, and ejection fraction. Student's t test for independent means was used to compare 6-min walk and peak oxygen consumption in NYHA class 3 and LVAS patients. To compare the LVAS patients who had multiple measurements, analysis of variance for repeated measures was used. The chi-square test was used for comparing categorical variables. Data are presented as mean ± SEM whenever appropriate.

The LVAS group included seven patients who received LVAS (Novacor, Palo Alto, Calif, model No. 1, n=6; Thoratec Lab, Berkeley, Calif, n=1) between October 1989 and December 1990. Patient age was 44±5 (range, 15 to 58) years. There were 6 men and 1 woman in this group. The etiology of the CHF was ischemic in 3 patients and nonischemic in 4 patients (idiopathic, n=3; and myocarditis, n=1).

The mean duration of implantation was 157±11 days (85 to 303 days). Six patients had successful cardiac transplantation, and one patient died on the device after 303 days. The CHF patients included a group of 121 NYHA class 3 and 81 NYHA class 4 CHF patients followed by our Heart Failure Unit between May 1982 and May 1991. No specific rehabilitation program was applied to the LVAS or NYHA class 3 patients. Class 3 patients were counseled to be as active as symptoms allowed without excessive fatigue. The LVAS patients were encouraged to walk and use a stationary bicycle which was present in the patient’s room.

<table>
<thead>
<tr>
<th>Feature</th>
<th>LVAS</th>
<th>NYHA Class 3</th>
<th>NYHA Class 4</th>
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<tbody>
<tr>
<td>Number</td>
<td>7</td>
<td>121</td>
<td>81</td>
</tr>
<tr>
<td>Age, yr</td>
<td>44±5</td>
<td>56±1*</td>
<td>57±1*</td>
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<tr>
<td>Sex, M/F</td>
<td>6/1</td>
<td>97/24</td>
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<tr>
<td>ICM/non-ICM</td>
<td>3/4</td>
<td>58/63</td>
<td>48/35</td>
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<tr>
<td>EF, %</td>
<td>19±2</td>
<td>22±1</td>
<td>19±1*</td>
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*Data are expressed as mean ± SEM.

p<0.05 vs LVAS

1ICM=ischemic cardiomyopathy; EF=ejection fraction.

p<0.05 vs NYHA class 3.

RESULTS

Patient group characteristics (Table 1) were comparable except that (1) LVAS patients were significantly (p<0.05) younger (44±5 years) than both NYHA class 3 (56±1 years) and 4 (57±1 years) patient groups and (2) the ejection fraction was significantly higher (p<0.05) in the NYHA class 3 (0.22±0.01) group compared with NYHA class 4 (0.19±0.01) patients. Although the preimplantation ejection fraction (0.19±0.02) in the LVAS patients was the same as that in NYHA class 4 patients, it was not statistically different from that of class 3 patients, as it was for the class 4 patients, probably due to the small number of LVAS patients.

Preimplantation LVAS resting cardiac output (3.8±0.1 L/min) on full pressor support (n=7) plus (n=5) intraaortic balloon pump, was significantly lower (p<0.001) than resting values obtained immediately after surgery (5.5±0.2 L/min), and at 1 (5.8

FIGURE 1. Comparison of mean ± SEM plasma levels of NE, PRA, and ANP in LVAS, NYHA class 3 (CHF 3), and NYHA class 4 (CHF 4) patients.
The results of this study demonstrate significant differences in neurohormonal activation and exercise capacity in patients who had implantation of a LVAS compared with groups of patients with severe heart failure. A previous study of three heart failure patients on asynchronous LVAS demonstrated improved exercise capacity as measured by oxygen consumption and increased cardiac output and heart rate during supine bicycle exercise 1 month after LVAS implantation.7

The level of sympathetic nervous system activation in heart failure may correlate with hemodynamic abnormalities, but this finding is not universally accepted.8 This activation may require “ergoreceptors” located in the skeletal muscle and kidneys and increased sympathetic outflow at rest related to attenuation of cardiopulmonary and arterial baroreflex afferent activity.9,10 This activation is reflected in an elevated plasma NE level, which in turn is probably due to both increased release and reduced uptake from adrenergic nerve endings.11

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these results with values of the NYHA class 3 group. The exercise tolerance in the LVAS group tended to improve progressively over time.

**Discussion**

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proves end-organ blood flow and allows resolution of multiorgan (renal, hepatic, and pulmonary) dysfunction in up to half of the patients on the device. The increased blood flow and the attenuation of the neurohumoral excitatory state may enhance baroreceptor responsiveness. Improvement in organ blood flow, particularly to the skeletal muscle and kidneys, will inhibit afferent sympathetic signals and decrease effenter nerve traffic.

The LVAS is likely responsible for a decrease in plasma renin activity by improved renal blood flow, inhibiting renin release from the afferent arteriole and decreasing sympathetic activation. The increase in sodium excretion also will inhibit renin release from the macula densa. The diminution in sympathetic nerve traffic to the juxtaglomerular apparatus will decrease sympathetically mediated renal renin release.

Plasma ANP levels are elevated and related to the clinical and hemodynamic severity of CHF, particularly the level of right and left atrial pressures.13 The LVAS completely unloads the left ventricle, thereby markedly decreasing left atrial stretch, reducing the primary stimulus to ANP release.13 By decreasing right ventricular outflow impedance, it may decrease right atrial pressure and stretch as well. Production of ventricular ANP in the heart failure state may add to overall plasma ANP levels, and relief of ventricular stress by LVAS may decrease the stimulus for its production.

The CHF patients have reduced peripheral blood flow during exercise due in part to reduced peripheral vasodilatory capacity.12 A decrease in blood flow may affect the vascular system itself.15 The depressed cardiac output in CHF patients results in a preferential decrease in limb blood flow that may lead to endothelium-mediated reduction in vessel diameter and dilatory capacity as has been demonstrated in humans and animal models with heart failure.16,17 The peripheral vasodilatory capacity also may be reduced due to prolonged immobilization.18 Deconditioning may mediate its effects on the peripheral vasculature by a chronic reduction in blood flow due to structural modifications of the arterial wall,19 the latter influencing the ability of the endothelial cells to release substances that cause relaxation of the vascular smooth muscle such as endothelial-derived relaxing factor.20 Skeletal muscle cell edema and interstitial volume overload may produce extravascular compression of capillaries and may limit arteriolar dilatation in the limbs and the maximal blood flow at the capillary level.21 Physical inactivity also produces muscle atrophy and decreased enzymatic activity22 that may be partially reversed once the patient becomes more active, and the imbalance between energy requirements and oxygen(substrate utilization in the skeletal muscle is partially corrected.

Inadequate oxygen delivery rapidly decreases intracellular pH which in turn determines muscle fatigue, induces excessive glycolysis, and activates metaboreceptors via lactate production that leads to a reduction in peak blood flow to the skeletal muscle.23-25 Intrinsic muscle and energy production abnormalities (shunting around capillary beds, block to diffusion, reduced mitochondrial oxidative capacity, and shift toward glycolysis dependence) and change in the fiber predominance, mass, or pattern of fiber recruitment have been suggested as other causes of exercise intolerance.22,24

The LVAS patients may improve exercise capacity by increasing muscle blood flow at rest. With the long-term relief of dyspnea at rest, the patients may attempt more activity, decreasing muscle deconditioning (the most likely responsible culprit for the intrinsic skeletal muscle abnormalities) and reversing endothelium-mediated skeletal muscle blood flow abnormalities.22,26 Similar results in exercise improvement have been observed weeks to months after successful heart transplantation.2,27 It may be that in CHF patients, localized or submaximal physical activity may cause both a chronic enlargement of the conduit blood vessels and an increase in the peak vasodilatory potential improving skeletal muscle perfusion as has been demonstrated in other populations such as trained athletes.18,28 These submaximal physical activities are not usually considered strong enough to produce other exercise-related conditioning adaptations.

Muscle wasting (“cardiac cachexia”) is present in as many as half of severely ill CHF patients29 who also have been shown to shift muscle fiber type distribution and reduce enzymatic activity for beta-oxidation of fatty acids.22 The LVAS patients may improve caloric and protein intake through better control of volume status, decrease in passive liver congestion, decrease in bowel wall edema leading to improved blood flow to the gut with better nutrient absorption, increase in feeling of well-being and less fatigue during the act of feeding, and probably return to the more bioenergetically effective skeletal muscle fibers.22 Further, improved exercise tolerance in LVAS patients may be related in part to decreased right ventricular filling pressure, a predictor of exercise capacity in both LVAS and CHF patients.30

Our study documents less severe neurohormonal activation and exercise intolerance in LVAS patients compared with severely ill heart failure patients. The LVAS appears to be a reasonable short-term alternative for circulatory support. These data suggest that if LVAS is to be considered for long-term use (chronic implantation), it has the capability, in addition to improving systemic blood flow, of favorably
affecting exercise and neurohormonal abnormalities
classictricant of the heart failure state and making
patients better candidates for cardiac transplantation.

ACKNOWLEDGMENT: We would like to express our sincere
appreciation to Mrs. Rhonda Oliver for the preparation of this
manuscript. In addition, we would like to thank Mrs. Tammy R.
Tokarczyk, RN, and Mrs. Yvonne M. Cannon, RN, Heart Failure
Unit research nurses, for their invaluable clinical contributions, to
Mr. Stephen Winowich and Mr. John Pristas, left ventricular as-
sist device engineers, to Ms. Carla Capretta, RN, left ventricular
assist device nurse coordinator, and to Mr. Alfred Cecchetti,
statistician for this project.

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