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SHORT REPORT

Sympathetic vasoconstrictor activity before and after left ventricular assist device implantation in patients with end-stage heart failure

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Aims Sympathetic overactivity, which predicts poor outcome in patients with heart failure, normalizes following cardiac transplantation. We tested the hypothesis that haemodynamic improvement following left ventricular assist device (LVAD) implantation is also associated with reductions in centrally generated sympathetic activity.

Methods and results In eight patients with heart failure (two women, six men, age 44–66 years), we continuously recorded electrocardiogram, beat-to-beat finger blood pressure, respiration, and muscle sympathetic nerve activity (MSNA) before and after implantation of the continuous-flow LVAD devices HeartWare HVAD ($n = 4$) and HeartMate II ($n = 2$), and the non-continuous-flow device HeartMate 3 ($n = 2$). LVAD implantation increased cardiac output by 1.29 ± 0.88 L/min ($P = 0.060$) and mean arterial pressure by 16.2 ± 7.9 mmHg ($P < 0.001$), while reducing pulse pressure by 25.3 ± 9.8 mmHg ($P < 0.001$). LVAD implantation did not change MSNA burst frequency (-1.3 ± 7.5 bursts/min, $P = 0.636$), total activity ($+0.62 \pm 1.83$ au, $P = 0.369$), or normalized activity ($+0.63 \pm 4.23$, $P = 0.685$). MSNA burst incidence was decreased (-7.8 ± 9.3 bursts/100 heart beats, $P = 0.049$). However, cardiac ectopy altered MSNA bursting patterns that could be mistaken for sympatholysis.

Conclusion Implantation of current design LVAD does not consistently normalize sympathetic activity in patients with end-stage heart failure despite haemodynamic improvement.

Keywords Heart failure • Left ventricular assist device • Microneurography • Sympathetic nerve activity • Baroreflex

Introduction

Sympathetic vasomotor tone[1] and plasma norepinephrine levels[2] predict mortality in patients with heart failure. A cross-sectional comparison between heart failure patients before and after cardiac transplantation suggested that transplantation may normalize sympathetic hyperactivity.[3] In a longitudinal study, cardiac transplantation lowered muscle sympathetic nerve activity (MSNA) which has been attributed to improved haemodynamics.[4] This can be explained, along with other factors, by Ohm's law of hydrodynamics, which implies that improved cardiac output via increased arterial pressure may reflexively lower sympathetic

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vasoconstrictor activity. In line with this, an inverse relationship between cardiac output and MSNA has been reported in healthy subjects[5] as well as in heart failure patients.[6] Left ventricular assist devices (LVAD) also improve haemodynamic function[7,8] and survival[9] in patients with end-stage heart failure. In cross-sectional samples, sympathetic activity was within the normal range in pulsatile- and non-pulsatile-flow LVAD patients.[10,11] Longitudinal studies suggesting decrease in sympathetic activity[8,12] did not directly measure sympathetic nerve activity.

We tested the hypothesis that LVAD implantation decreases centrally generated sympathetic vasoconstrictor nerve activity in patients with end-stage heart failure in a longitudinal study design. To be able to assess the time course of sympatholysis, we sought to investigate patients twice, namely early and late, after LVAD implantation.

Methods

Of 22 patients with end-stage heart failure with reduced ejection fraction who had been considered for LVAD implantation, eight were available for MSNA measurements before and after implantation (two women, six men, age 56 ± 8 years, body mass index 25.5 ± 4.8 kg/m^2, ejection fraction 10–25%). Four patients had been diagnosed with dilated and four patients with ischaemic cardiomyopathy. Two patients featured obstructive and one patient central sleep apnoea. All patients were on diuretics and renin–angiotensin system inhibitors. Seven patients were on beta-blockers. Patients on inotropic medications, e.g. levosimendan, were excluded. The investigation conformed with the principles outlined in the Declaration of Helsinki. The Hannover Medical School Review Board approved the study (approval #5097) and written informed consent was obtained from the patients before study entry.

We conducted measurements during supine rest after an overnight fast in the morning hours before and again early and/or late following LVAD implantation. All measurements were conducted with the patients in a stable state, i.e. without left or right heart decompensation, bleeding, or infection. Without any physical exercise, aortic valves open only sporadically as in the majority of our post-implant measurements.[13] As is common practice in post-operative care, LVAD speed adjustments in our patients ensure valve opening at least intermittently. Four patients were able to follow the pattern of inert gas rebreathing for non-invasive determination of cardiac output (Innocor, Innovision, Odense, Denmark). We continuously recorded electrocardiogram, beat-by-beat finger blood pressure (Finometer Midi, Finapres Medical Systems, Amsterdam, The Netherlands), and impedance cardiogram (Niccomo, Medis GmbH, Ilmenau, Germany) to assess O-wave amplitude, a non-invasive measure for left ventricular dysfunction.[14] We obtained MSNA from the right peroneal nerve (Nerve Traffic Analyzer 662C-3, University of Iowa, Iowa City, IA, USA) using unipolar tungsten electrodes. Because arrhythmic events are numerous in these patients, we did not exclude event-related sympathetic bursts (online supplementary *Figure S1*). Data are expressed as mean ± standard deviation. Differences were compared by paired *t*-tests. *P*-values <0.05 were considered statistically significant.

Results

Four patients were implanted with a HeartWare (Medtronic, Minneapolis, MN, USA), two with a HeartMate II, and two with a HeartMate 3 device (Abbott, Pleasanton, CA, USA). In all patients, we obtained good quality MSNA recordings before and after implantation. Early and late measurements took place 8–22 days post-implantation, when the patients were still hospitalized but in a steady state, and 185–725 days post-implantation during outpatient care, respectively. In two patients, we obtained both, early and late measurements following implantation (Patients #5 and #6 in *Figure 1*). In three patients, early measurements were not possible due to concomitant clinical issues. One patient had died and in one patient LVAD-generated electrical noise obscured nerve recordings. *Table 1* reports individual medications and LVAD settings for all pertinent measurements. For instance, except for Patient #5, all patients were on beta-blocker therapy during all measurements.

Haemodynamics and MSNA before and after LVAD implantation are presented in *Table 2*.[15,16] Cardiac output, mean arterial pressure, and O-wave amplitudes were all improved following LVAD implantation while heart-generated pulse pressure significantly decreased. MSNA was substantially elevated in most patients before implantation. Yet, MSNA responses to LVAD implantation were heterogeneous (*Figure 1*). We did not observe major MSNA reductions regardless of LVAD type; diamonds in *Figure 1* denote patients with pulsatile LVAD.

In online supplementary *Figure S1*, original recordings from Patient #5 illustrate in an exemplary way how clinical consequences of severe heart failure affect sympathetic bursting patterns. The patient showed high MSNA, Cheyne–Stokes breathing, and occasional ectopic beats before LVAD implantation. LVAD implantation increased cardiac output ~1.0 L/min and mean blood pressure ~19 mmHg, and Cheyne–Stokes respiration disappeared. Eleven months after implantation (late post-implant), the patient showed bigeminy with increased pulse pressure and reduced number of sympathetic bursts. However, this must be seen as spurious sympatholysis as these bursts were larger indicating an increased number of action potentials per sympathetic burst (online supplementary *Figure S1* and Patient #5 in *Figure 1C*).

Conclusion

The important finding of our longitudinal study is that haemodynamic improvements following LVAD implantation do not consistently translate to major reductions in central sympathetic outflow. The finding contrasts with cross-sectional data in patients implanted with continuous-flow LVAD, which showed increased[10] or normal sympathetic activity.[11] Normalization of sympathetic overactivity after cardiac transplantation has been attributed to restored haemodynamic function.[4,17] LVAD-generated pulsatility may[18] or may not be important for baroreflex-mediated sympathetic inhibition.[11] HeartMate 3 incorporates a pulse-mode algorithm, which involves automated modulations in pump speed, but data are lacking to suggest that this imparts a physiologic pulse. The two patients who have been implanted with the device did not fare better.

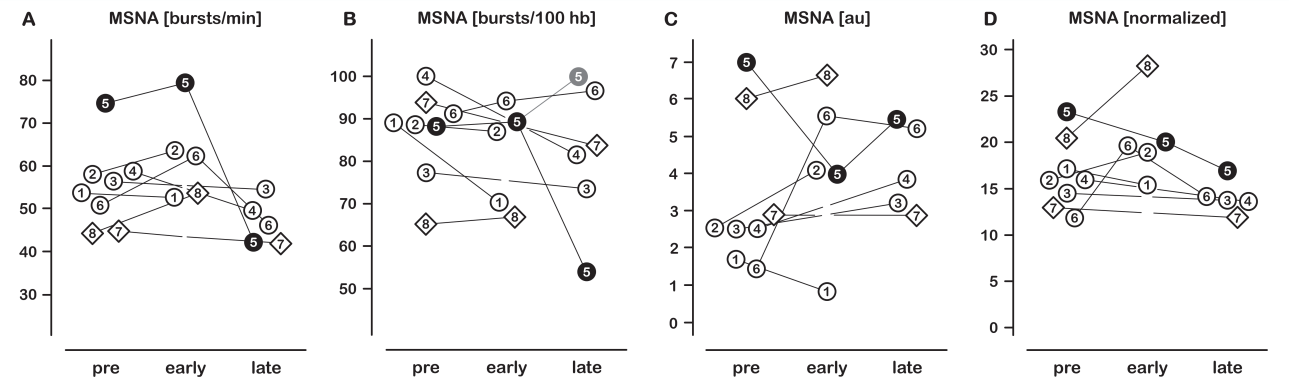

Figure 1 Individual sympathetic activities before, early, and late after left ventricular assist device (LVAD) implantation. Diamonds represent Patients #7 and #8 with pulsatile LVAD. Patient #5 data are depicted as filled circles: note the misleading decrease in burst frequency and incidence during late post-implant measurement which is caused by bigeminal rhythm. If related to haemodynamically effective heartbeats, muscle sympathetic nerve activity (MSNA) burst incidence was virtually 100 bursts/100 heart beats (*B*, grey data point, Patient #5; see online supplementary *Figure S1* for detailed information).

Table 1 Cardiovascular medication and left ventricular assist device parameters

	Patient # Pre/Early/Late							
	1 PEL	**2 PEL**	**3 PEL**	**4 PEL**	**5 PEL**	**6 PEL**	**7 PEL**	**8 PEL**
Beta-blocker	●●□	●●□	●□●	●□●	○●●	●●●	●□●	●●□
AT1 blocker, ACE inhibitor	●●□	●●□	●□○	●□●	●○○	●●●	●□●	●●□
Aldosterone antagonist	●●□	●○□	●□○	●□●	○○●	○○○	●□●	●●□
Thiazide diuretic	●●□	●○□	●□○	○□●	●●○	○○○	●□●	○○□
Loop diuretic	●●□	●○□	●□●	●□●	●●●	●●●	●□●	●●□
Antiarrhythmic	●●□	●●□	●□○	●□○	●○○	○○○	○□○	○○□
Statin	○○□	○○□	●□●	●□○	●○○	●●●	○□○	●●□
Platelet aggregation inhibitor	○●□	○●□	●□●	○□●	●●●	○●●	●□●	●●□
Anticoagulant	●●□	●●□	○□●	●□●	○●●	○●●	○□○	○●□
Speed (rpm)	3000	2600	2840	2920	2480[a]	2600[a]	5700	5600
Flow (L/min)	5.3	4.9	6.3	6.9	4.8/4.4	4.3/3.1	4.1	4.1
Power (W)	5.8	3.7	5.0	5.6	3.2/3.1	3.5/3.3	4.4	4.4
Pulsatility index							5.6	5.6

Patients on inotropic medications, e.g. levosimendan, were excluded. None of the aortic valves have been oversewn.
P/E/L, pre-implant/early post-implant/late post-implant measurement.
●, intake; ○, no intake; □, no measurement.
[a]On both post-implant occasions.

Heart failure is characterized by heterogeneous changes in afferent, central, and efferent autonomic neuromodulation,[19] rendering individual net results of LVAD implantation hard to predict. For instance, the proportional characteristic of baroreceptors inhibits sympathetic outflow with increased mean arterial pressure, while their differential property counteracts sympatholysis because of reduced pulse pressure (*Table 2*).[20] Moreover, depending on the pre-implant activity of paradoxical sympathoexcitatory cardiopulmonary afferents, LVAD implantation may or may not mitigate sympathetic tone.[21] Sympathoexcitation may also result from cardiac dysrhythmias and changes in respiratory control, which may persist after LVAD implantation. Furthermore, afferents from the remaining diseased hearts could maintain sympathetic activation.[22] Heart failure is accompanied not only by autonomic but also by humoral disturbances. For instance, arginine vasopressin levels are significantly elevated,[23] the vasoconstrictor action of which is most likely counteracted by some degree of sympathoinhibition.[24] Cardiac transplantation or LVAD implantation lower arginine vasopressin levels[23] which can be expected to increase MSNA. Cardiac remodelling, deteriorated

Table 2 Comparison of haemodynamics and sympathetic activity before and after left ventricular assist device implantation

Parameter	Pre-implant ($n = 8$)	Early post-implant ($n = 5$)	Late post-implant ($n = 5$)	Mean post-implant	*P*-value
Haemodynamics					
CO (L/min)	2.58 ± 0.67	4.56 ± 0.76	3.56 ± 1.53	3.87 ± 1.18	0.060
SBP (mmHg)	79.5 ± 13.9	79.5 ± 8.9	78.6 ± 15.2	79.9 ± 11.1	0.905
MBP (mmHg)	56.4 ± 8.5	74.8 ± 7.8	68.3 ± 11.8	72.6 ± 8.2	<0.001
DBP (mmHg)	44.9 ± 6.6	72.9 ± 7.4	66.0 ± 13.4	70.7 ± 9.5	<0.001
HR (bpm)	65.9 ± 10.8	77.2 ± 8.7	64.0 ± 14.9	70.3 ± 11.9	0.082
PP (mmHg)	34.6 ± 9.6	6.7 ± 2.3	12.5 ± 5.5	9.3 ± 4.1	<0.001
PP7 (mmHg)	47.4		24.8	24.8	
PP8 (mmHg)	39.9	25.3		25.3	
O-wave (mOhms/s)	627 ± 211	273 ± 102	305 ± 203	264 ± 127	0.001
MSNA (burst frequency, burst incidence, total activity, normalized total activity)					
MSNA (bursts/min)	55.0 ± 9.6	62.2 ± 10.8	46.6 ± 5.5	53.7 ± 6.7	0.636
MSNA (bursts/100 heart beats)	86.6 ± 10.7	81.6 ± 12.1	78.0 ± 15.7	78.8 ± 9.7	0.049/0.198*
MSNA (au)	3.34 ± 2.04	4.23 ± 2.20	4.13 ± 1.17	3.96 ± 1.75	0.369
MSNA (normalized)	16.5 ± 3.8	20.4 ± 4.7	14.1 ± 1.8	17.1 ± 5.1	0.685

Values are given as mean ± standard deviation.
au, arbitrary units; CO, cardiac output ($n = 4$); DBP, diastolic blood pressure; HR, heart rate; MBP, mean blood pressure; MSNA, muscle sympathetic nerve activity; normalized, relative to largest burst; PP, pulse pressure; PP7/8, artificial pulse pressures in Patients #7 and #8 with pulsatile left ventricular assist device; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion.
TAPSE was >12 mm in all patients indicating stable right ventricular function[15] (for unassisted hearts, TAPSE cutoff is 17 mm[16]).
P-values for mean post- vs. pre-implant.
**P*-value for alternative burst incidence calculation of Patient #5 (100 bursts/100 pulses instead of 54 bursts/100 heart beats).

pump function, and sympathetic activation constitute a vicious cycle.[25] In patients whose device could be explanted, myocardial recovery and catecholamine reduction were strongly correlated.[26] Hence, timing of LVAD implantation may have a bearing on sympathetic activity and the outcome.[27] It remains to be determined if LVAD designs, which lower sympathetic overactivity by generating a more physiological pulse, improve outcomes in patients with potentially reversible myocardial dysfunction or when LVAD implantation is considered as destination therapy.

Our study has limited statistical power because of the small sample size. As end-stage heart failure patients are difficult to study, we hope for a more complete picture when data from different laboratories can be taken into account. Large variability in sympathetic nerve activity is another weakness, which possibly arises from the heterogeneity of patients' medical histories, responses to LVAD, implanted devices and their consequences for arterial baroreceptor stimulation and entrainment of outflow, and post-implant study dates. LVAD implantation decreased plasma norepinephrine levels in some studies[12,26] but not in others.[28] Because we did not measure plasma or myocardial catecholamine levels, we cannot extrapolate our findings to districts other than skeletal muscle which, however, may have prognostic value by itself.[1] Furthermore, we cannot exclude that changes in medications may have confounded our analysis. Finally, we do not know whether sympathoexcitation would diminish in patients with myocardial recovery.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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