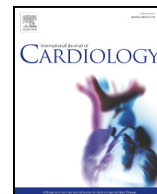




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Cardiovascular autonomic control in patients undergoing left ventricular assist device (LVAD) support and pharmacologic therapy

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ABSTRACT

Objectives: The objective of the study is to determine cardiac autonomic control in patients undergoing assessment for and/or LVAD therapy.

Methods: Heart rate variability (HRV) was measured in 17 explanted LVAD, 17 implanted LVAD and 23 NYHA III–IV classified chronic heart failure (CHF) patients and ten healthy matched controls under three conditions: supine free breathing, standing and supine controlled breathing. Five measures of HRV were assessed: mean R–R interval (mR–R), high frequency (HF) and low frequency (LF) spectral power, LF in normalised units (LFnu), and LF to HF (LF:HF) ratio.

Results: Repeat measures ANOVA showed significant ($p < 0.05$) differences in HRV between all three conditions within groups. Lower values were observed in CHF for LF (in log natural units) compared with explanted patients (-1.4 [95% CI -2.6 to -0.7], $p = 0.04$) and controls (-2.1 [-3.5 to -0.7], $p = 0.001$) and for LF:HF compared with implanted patients under paced breathing conditions ($z = -2.7$, $p = 0.007$) and controls in standing ($z = -2.9$, $p = 0.004$) and paced breathing conditions ($z = -2.3$, $p = 0.02$). However, no significant differences were seen between explanted, implanted and control groups under any condition.

Conclusions: Patients implanted with an LVAD and explanted from a LVAD following myocardial recovery demonstrate a more normal dynamic response to autonomic stimuli and have a lower HRV risk profile compared to CHF patients.

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1. Introduction

Chronic heart failure (CHF) is a complex, multifactorial syndrome characterised by: inadequate tissue perfusion, fluid retention, skeletal muscle abnormalities, progressive activation of the neuroendocrine system (e.g. RAAS) and inappropriate immune response [1]. CHF patients demonstrate severe derangement of the autonomic nervous system (ANS) [2,3] characterised by chronic sympathetic hyperactivation [2], vagal withdrawal [3], resetting of the baroreflex sensitivity [4] and decreased peripheral and central responsiveness to adrenergic input [5].

This chronic sympathetic activation manifests as greatly altered heart rate variability (HRV). Overall R–R interval variation is lower in CHF patients who die compared with survivors [6–8]. Spectral

analysis of HRV produces a characteristic HRV profile in CHF with attenuated variability both in the low frequency (LF, 0.04–0.15 Hz) and reduced low-to-high frequency ratio (LF:HF) which both predict patient mortality [9,10].

Historically, the only cure for end stage CHF has been transplantation. In post-transplant patients, there is some restoration in autonomic modulation of the native sinus node. While there is also some evidence for partial (sympathetic) reinnervation of the donor heart, autonomic control and HRV remain well below normal levels [11].

Using left ventricular assisting devices (LVADs) to bridge patients to transplantation, destination therapy [12], or recovery [13] has become successful practise [14]. In combination with optimal pharmacotherapy, our group has been able to reverse many of the pathological changes associated with end stage heart failure and up to two thirds of patients with dilated cardiomyopathy can be explanted [15]. These patients may avoid transplantation and tend to lead higher quality lives than transplant patients [16].

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Sudden cardiac death (SCD) remains the most likely mode of death for CHF patients [17] due to autonomic dysfunction and poor innervations respectively. While cardiac function and exercise capacity [18] of explanted LVAD patients exceed that of CHF sufferers, it remains unknown whether the same is true for cardiac autonomic function.

The aim of the present study was to assess the impact of 'bridging to recovery' on autonomic function in patients diagnosed with end stage heart failure undergoing assessment for and/or LVAD support therapy.

2. Methods

2.1. Patients

Heart rate variability was assessed in an opportunity sample of 17 explanted LVAD patients (age 36 ± 11 years, 12 men), 17 currently implanted patients (33 ± 10 years, 16 men), 23 NYHA III–IV classified chronic heart failure (CHF) patients (42 ± 12 years, 13 men) and ten healthy, age- and sex-matched controls from hospital and university staff (37 ± 12 years, 8 men). Assessments took place over the period of January 2004 to July 2008, therefore LVAD previously implanted in the explanted patients consisted of: a HeartMate 1 ($n = 8$); a HeartMate 2 ($n = 5$) (Thoratec Corporation, Pleasanton, CA, USA) a Levitronix ($n = 1$) (Thoratec Corporation, Pleasanton, CA, USA), a Heartware ($n = 1$) (Heartware, Miami, USA) or a Jarvik 2000 (Jarvik Heart Inc. NY, USA, $n = 2$). All patients had been implanted only once but one had received additional right ventricular assistance from a Thoratec VAD (Thoratec Corporation, Pleasanton, CA, USA). In twelve explanted patients, the original diagnosis was idiopathic dilated cardiomyopathy (IDCM), in four it was peripartum cardiomyopathy and one had myocarditis.

Currently implanted LVAD patients had: a HeartMate 1 ($n = 4$); a HeartMate 2 ($n = 7$); a Heartware ($n = 1$); a Jarvik 2000 ($n = 3$), or a Thoratec ($n = 2$). Twelve patients had IDCM, one peripartum cardiomyopathy, three ischaemic heart disease (IHD), and one had myocarditis.

Of the CHF patients, 11 were diagnosed with IDCM, four with peripartum cardiomyopathy, six with IHD and two had myocarditis. Further anthropometric, physiological and pharmacological data are displayed in Table 1.

The control group was matched for age and sex with the explanted LVAD patient group. All controls were either sedentary or moderately physically active. None had a history of cardioneuroregulatory disorders. None were taking any prescribed medications, with the exception of oral contraceptives, at the time of testing. Due to the oligomenorrhoeic nature of the female CHF patients, menstrual cycle phase was not controlled for in this group or their matched controls.

The local NHS ethics committee approved the research protocol and informed consent was obtained from all participants. The investigation conforms with the principles outlined in the Declaration of Helsinki.

Table 1

Descriptive characteristics of implanted and explanted LVAD patients.

	CHF	Implanted	Explanted	Control
N	23	17	17	10
Males/females	13/10	16/1	12/5	8/2
Age (years)	42.3 ± 12.1	32.8 ± 10.2	36.2 ± 10.9	37.0 ± 12.2
Mass (kg)	82.1 ± 19.5	78.7 ± 19.4	86.7 ± 24.9	87.2 ± 13.0
Stature (cm)	168.6 ± 11.4	180.4 ± 8.5	176.1 ± 12.0	178.2 ± 11.4
BMI ($m^2 \cdot kg$)	29.0 ± 7.7	24.0 ± 4.8	27.6 ± 5.7	27.3 ± 1.7
BSA (m^2)	1.93 ± 0.48	1.98 ± 0.55	2.18 ± 0.70	2.17 ± 0.43
Time from explant/implant/diagnosis (days)	1291 ± 1577	184 ± 136	718 ± 639	n/a
NYHA class	3.3 ± 0.7	1.8 ± 0.7	1.1 ± 0.3	n/a
LVEF at time of test (%)	39.5 ± 14.2	47.8 ± 9.4	62.6 ± 13.3	n/a
<i>Aetiology (number)</i>				
IDCM	11	12	12	n/a
IHD	5	3	0	n/a
MYO	3	1	1	n/a
PP	4	1	4	n/a
Clenbuterol treatment (%)	0	25	100	n/a
Clenbuterol at time of test (%)	0	6	0	n/a
Digitalis (%)	27	38	100	n/a
β -Blockers (%)	64	87	87	n/a
ACE-inhibitors (%)	27	62	100	n/a
ARB (%)	58	62	87	n/a
Spirolactone (%)	41	50	62	n/a
Other (%)	60	87	38	n/a

BMI—body mass index, BSA—body surface area, EF—ejection fraction, IDCM—idiopathic dilated cardiac myopathy, IHD—ischaeamic heart disease, MYO—myocarditis, PP—post-prandial heart failure, ACE—angiotensin converting enzyme, ARB—angiotensin receptor blocker. All pharmacological data refer to whether patients were prescribed with the drug type at time of HRV measurement except clenbuterol treatment – refers to whether the patient had ever received clenbuterol; n/a—non-applicable.

2.2. Instrumentation

Two lead ECGs were recorded using a TF5 heart rate variability analysis system (Advanced Medical Diagnostics Ltd., Leeds, UK). This is a commercially available unit, which is mobile as well as being relatively simple and quick to fit to patients. The hardware and software components of the TF5 and its comparative validity with a 12 lead ECGs have been described previously [19]. The TF5 HRV analysis software was used to analyse the R–R interval data via fast Fourier transformation. All recording and analysis protocols surpass the criteria for sampling rates, conversion rates and mathematical treatment of data for HRV analysis [20].

2.3. Protocol

After fitting the patients with the TF5 chest strap in accordance with manufacturers' instructions, patients were allowed resting supine for 5-min. After this time, 5-min ECGs were recorded in three conditions: supine with free breathing, standing and supine with controlled breathing at $12 \text{ breaths} \cdot \text{min}^{-1}$. The supine condition was used as a baseline measure of resting autonomic modulation. The standing condition was used to represent orthostatic challenge, known to evoke sympathetic responses in healthy subjects. Finally the controlled breathing condition was used to stimulate vagal modulation of the SA node. We have reported the validity and reliability of this testing protocol in healthy participants previously [19]. All R–R interval data were first filtered using the automated algorithms available in the software. Additional manual ECG analysis, non-sinus beat rejection and consequent interpolation were also performed by a highly experienced HRV researcher.

All HRV measures recommended for use during short-term data collection were calculated [20]. In the frequency domain: high frequency spectral power (HF, 0.15–0.40 Hz), low frequency spectral power (LF 0.04–0.15 Hz) normalised low and high frequency spectral power (LFnu, HFnu), and the ratio of low to high frequency spectral power (LF:HF). In the time domain: mean R–R interval, standard deviation or normal-to-normal intervals (SDNN) and the root mean square of successive interval differences (rMSSD) were measured.

2.4. Statistical analysis

Two-way mixed (group by position) analysis of variance was used to determine whether differences between conditions (i.e. position and breathing) and between control, CHF, implanted and explanted patients (group) existed. Analysis was carried out on HRV measures representative of vagal modulation (HF), mixed sympathovagal and baroreflex activity (LF) and its normalised units (LFnu), sympathovagal interaction (LF:HF) and mean R–R interval. Due to heterogeneous variances and non-normal distributions which could not be modified successfully by transformation, LF:HF was analysed using repeated nonparametric Kruskal–Wallis tests ($n = 3$) with post-hoc Mann–Whitney U tests. For all tests, a two-sided value of $p < 0.05$ was considered statistically significant. We present data as mean \pm SD and the 95% confidence interval/limits (CI) for the mean to demonstrate the magnitude of effects across each of the groups.

Further non-statistical comparisons were made by comparing mean (\pm SD) levels of significant short-term HRV risk factors reported previously [9,10] with values obtained for explanted, implanted and CHF patients and for comparison, control subjects. This analysis allowed visual evaluation of spectral HRV profiles at different points during 'bridging to recovery' in comparison with heart failure patients and healthy control individuals.

3. Results

Table 1 provides the descriptive characteristics of the implanted, explanted and CHF patient groups. Implanted and explanted patients were similar in terms of age and anthropometric measures, disease aetiology, and geometric echocardiographic measures. The CHF patients were older and some differences in pharmacotherapy existed between groups, particularly in the frequency of use of clenbuterol.

3.1. Comparisons between patient groups and healthy controls

Table 2 shows the changes in R–R interval, HF power as natural logarithm (\ln ms²), LF(\ln) and LF:HF under supine, standing and supine controlled breathing conditions in implanted, explanted and CHF patients and healthy controls.

Repeated measures ANOVA showed significant ($p < 0.05$) differences for all three conditions within groups. There were significant group differences across conditions for LF in log transformed (LF(\ln), $p = 0.02$) and normalised units (LFnu, $p = 0.01$) and for LF:HF ($p = 0.007$) in the paced breathing condition only. There were no significant between group differences in R–R interval ($p = 0.08$) or HF(\ln) ($p = 0.13$). Post-hoc analyses demonstrated that nearly all group differences were between the CHF patients and one or more of the remaining three groups as follows: significantly lower values for LF(\ln) compared with explanted patients (-1.4 [95% CI -2.6 to -0.7], $p = 0.04$) and controls (-2.1 [-3.5 to -0.7], $p = 0.001$); for LFnu compared with implanted (-19.4 [-38.1 to -0.5], $p = 0.04$) and controls (-20.3 [-38.6 to -1.9], $p = 0.03$); and for LF:HF compared with implanted patients under paced breathing conditions ($z = -2.7$, $p = 0.007$) and controls in standing ($z = -2.9$, $p = 0.004$) and paced breathing conditions ($z = -2.3$, $p = 0.02$).

Due to the relatively small number of patients available, a visual analysis of changes in LF:HF ratio due to standing and controlled breathing was also performed. Fig. 1 shows the expected increase in LF:HF due to standing compared with values measured in the supine

position in control, heart failure and implanted and explanted patients. The pattern of change was similar in both implanted and explanted patients and their values were more closely matched to those of the control group compared to those of CHF patients.

4. Discussion

The aim of this study was to examine the potential of LVAD unloading and optimal pharmacotherapy to alter cardiac autonomic nervous system activity in end-stage heart failure patients, a condition typically characterised by severe autonomic derangement. In explanted patients, our power-spectral analysis of HRV demonstrated patterns of cardiac ANS activity that were similar to those of healthy, age-matched controls.

Successful explantation is the desired clinical endpoint for LVAD patients who are 'bridged to recovery' [13,14] and although not all patients achieve this some degree of reverse modelling occurs in most [21]. The present data show that in currently implanted LVAD patients, there appears to be a partial normalisation of the HRV profile as we found no difference between controls and implanted patients for mean R–R interval or spectral HRV values.

4.1. Low frequency spectral power: explants and implants

The characteristic HRV profile of heart failure patients shows severely attenuated overall variability, particularly in the low frequency spectral component (LF, 0.04–0.15 Hz). Values for LF predictive of mortality range from 3.3 \ln ms² from Holter recordings [22] to between <13 ms² [9] and 20 ms² [10] when extracted from more-stationary recordings as in the present study. We have previously calculated estimated normal values for the LF frequency component to be around 519 ± 219 ms² or 5.0 ± 1.8 \ln ms² [23]. HRV measures should be compared only between comparable R–R interval recording conditions and the following discussion relates to data collected supine with free breathing.

Mean LF power in our controls was within the normal range. Remarkably however, and despite having been previously diagnosed with end-stage heart failure, mean LF values of explanted patients were similar to that of controls and therefore population norms. Perhaps more importantly, both mean and the lower 95% CI (4.7 [3.7 to 5.8]) values were well in excess of values known to predict mortality in CHF. While we do not have longitudinal data to describe the changes in HRV from pre-implantation to explantation, it is clear that LF power

Table 2

Vales for mean R–R interval, high frequency (HF) and low frequency (LF) spectral power and LF:HF ratio under three conditions in healthy controls, heart failure, implanted and explanted LVAD patients.

	Heart failure	Implanted	Explanted	Control
<i>Measures obtained supine</i>				
mR–R(ms)	911 \pm 334 (686 to 1135)	804 \pm 132 (702 to 905)	890 \pm 104 (827 to 953)	947 \pm 123 (858 to 1035)
LF(\ln)	4.2 \pm 1.7 (3.0 to 5.4)	5.0 \pm 1.4 (3.9 to 6.0)	5.6 \pm 1.5 (4.6 to 6.5)	6.3 \pm 1.6 (5.3 to 7.2)
HF(\ln)	4.1 \pm 2.1 (2.7 to 5.5)	4.2 \pm 1.4 (3.1 to 5.3)	5.4 \pm 0.9 (4.8 to 5.9)	5.5 \pm 1.3 (4.6 to 6.4)
LF(nu)	52 \pm 23 (37 to 68)	68 \pm 12 (59 to 77)	53 \pm 26 (38 to 69)	66 \pm 17 (53 to 78)
LF:HF	1.8 \pm 1.9 (0.6 to 3.1)	3.2 \pm 3.2 (0.6 to 5.5)	2.6 \pm 3.5 (0.4 to 4.9)	3.4 \pm 3.6 (0.6 to 6.0)
<i>Measures obtained standing</i>				
mR–R(ms)	759 \pm 145 (662 to 857)	694 \pm 82 (631 to 757)	766 \pm 78 (719 to 813)	795 \pm 81 (737 to 853)
LF(\ln)	3.8 \pm 1.1 (3.1 to 4.6)	4.8 \pm 1.4 (3.7 to 5.8)	4.7 \pm 1.2 (4.0 to 5.4)	6.0 \pm 1.2 (5.2 to 6.9)
HF(\ln)	3.5 \pm 1.9 (2.3 to 4.8)	3.7 \pm 1.5 (2.6 to 4.9)	3.7 \pm 1.1 (3.0 to 4.3)	4.2 \pm 1.4 (3.2 to 5.2)
LF(nu)	56 \pm 25 (39 to 73)	74 \pm 20 (58 to 89)	74 \pm 17 (64 to 84)	85 \pm 5 (81 to 89)
LF:HF	2.5 \pm 2.7 (0.7 to 4.3)	5.3 \pm 5.2 (1.3 to 9.3)	4.9 \pm 4.9 (1.6 to 7.8)	7.0 \pm 5.6 (3.1 to 11.4)
<i>Measures obtained supine with controlled breathing</i>				
mR–R(ms)	858 \pm 210 (717 to 999)	770 \pm 121 (677 to 862)	890 \pm 97 (832 to 949)	978 \pm 113 (898 to 1059)
LF(\ln)	3.6 \pm 1.6 (2.5 to 4.7)	4.8 \pm 1.2 (3.9 to 5.7)	5.4 \pm 1.5 (4.5 to 6.3)	5.6 \pm 1.3 (4.7 to 6.5)
HF(\ln)	4.5 \pm 2.4 (2.9 to 6.1)	4.6 \pm 1.5 (3.4 to 5.7)	6.1 \pm 1.4 (5.4 to 7.0)	5.6 \pm 1.2 (4.7 to 6.5)
LF(nu)	32 \pm 25 (15 to 49)	56 \pm 21 (40 to 72)	35 \pm 24 (21 to 50)	50 \pm 23 (33 to 66)
LF:HF	0.7 \pm 1.1 (0.0 to 1.9)	1.4 \pm 1.2 (0.8 to 2.9)	0.8 \pm 0.9 (0.3 to 1.4)	1.6 \pm 1.5 (0.4 to 2.7)

All data are mean \pm standard deviation with 95% CI for the mean in parentheses; ms – milliseconds; nu – normalised units; \ln – log units; controlled breathing was performed at 12 breaths \cdot min⁻¹.

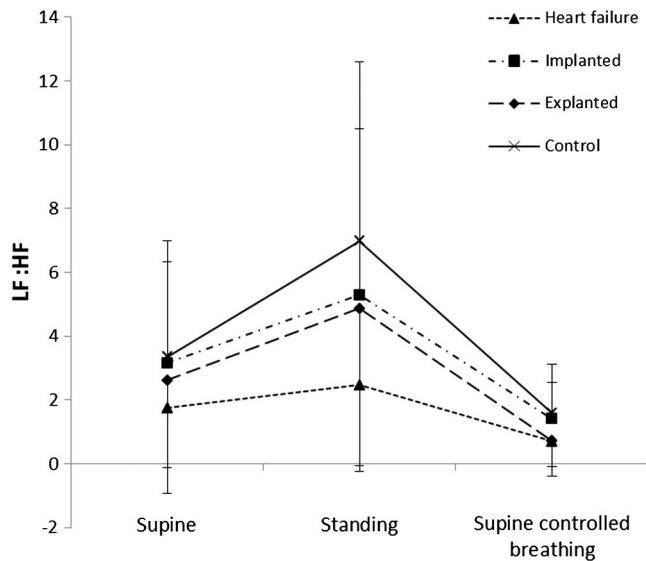


Fig. 1. LF:HF ratio values in LVAD implanted, LVAD explanted and chronic heart failure patients and controls.

of both explanted and currently implanted patients is much more similar to normal values than to the heart failure patients measured here. Explanted and currently implanted LVAD patients therefore demonstrate a lower HRV risk profile compared with chronic heart failure patients. If we assume that implanted and explanted patients' LF values were similar to those of the heart failure group prior to LVAD therapy, their current, near-normal levels demonstrate the potential for autonomic recovery following our treatment programme.

4.2. Low to high frequency ratio: explants and implants

We analysed the ratio of low to high frequency powers (LF:HF) ratio to evaluate the interaction between both ANS branches. It should, however, be noted that the conditions under which the behaviour of LF:HF actually matches sympathetic activation and/or vagal withdrawal are somewhat limited [24]. Interpretation of LF:HF in patients demonstrating severe autonomic derangement is particularly problematic [2,3]. Whereas in healthy populations LF:HF usually reflects an increase in sympathetic outflow (and/or vagal withdrawal) values in LF:HF and in CHF patients with excessive sympathetic outflow is, paradoxically, very low. This is because of very low values for LF due to severely attenuated baroreflex sensitivity in these patients [25]. Regardless of its physiological meaning, low LF:HF is a risk factor of mortality and cardiac event in CHF patients [9,10]. The reduced LF component in the HRV profile of CHF patients results in a low LF:HF ratio and the most sensitive values to predict mortality reported by La Rovere et al. were <0.37 and <0.43 [9].

In the present study, values for LF:HF were much higher and almost identical in explants, implants and controls. LF:HF showed great intra-individual variation and while the lower 95% CI in explants was below the cut-point of La Rovere et al. [9], this was not the case in implanted patients and the mean values in both cases do not suggest that these patients are at significantly heightened risk of SCD [10]. From these data, we propose that the balance between LF and HF power is likely to be partially restored in CHF patients during LVAD support and that this restoration of balance is maintained post-explantation.

4.3. Autonomic response to standing and controlled breathing

The response of HRV measures to orthostatic challenge and deep breathing has not been used in prognosis in CHF patients, however it remains a useful tool by which to assess dynamic control of ANS. Typically,

this is deranged in CHF patients and we aimed to determine whether a normal profile of change in HRV measures had returned in LVAD patients. Standing comprises an orthostatic challenge, the autonomic response to which is typified by a reproducible decreased HF and increased LF contribution to total spectral power [26]. The use of controlled breathing typically increases the vagal contribution to SA node control [27]. CHF patients with sympathetic hyperactivity tend to show blunted decreases in vagal indices (HF, HFnu) and increases in indices (LFnu) of sympathetic activation [26]. While this was the case in our CHF patients, the LF:HF for implanted and explanted patients displayed a typical response to standing (increase) and decreased under the increased vagal outflow created by controlled breathing (Fig. 1). Even the magnitudes of these changes were highly similar between groups the increase in LF:HF upon standing demonstrates combined vagal withdrawal and sympathetic activation (increased relative LF contribution) mediated via the baroreflex. These are the first data, therefore, to demonstrate a normalisation of HRV indices recorded under resting conditions that indicate a reduced likelihood of cardiac events in currently implanted and explanted LVAD recipients. These data are also the first to demonstrate normality of the dynamic autonomic responses to simple sympathetic and vagal perturbations.

4.4. Potential mechanisms of recovery

The unloading of the failing myocardium by LVAD implantation, combined with optimal pharmacotherapeutic interventions results in multiple favourable physiological changes including partial restoration of hemodynamic responses to exercise [18], 'reverse remodelling' [28] of the myocardium which has been well described at both macrostructural [29] and cellular levels [30]. Burkhoff et al. [29] suggest restoration of the 'normal neurohormonal milieu' is a precursor to such adaptations but descriptions of this autonomic normalisation are scarce. Scintigraphy demonstrates that hemodynamic improvements are accompanied by improved sympathetic innervation of failing myocardium in implanted patients [31]. Changes in sympathetic innervation correlate improvements in clinical measures including B-type natriuretic peptide and pulmonary systolic pressure [32]. LVAD implantation may increase myocardial noradrenalin via the renin-angiotensin-aldosterone pathway [30] but the optimised pharmacotherapy [15] in these patients reduces or negates this change. No group has yet published data describing changes in integrated cANS function (sympathovagal interaction) associated with LVAD therapy.

In addition to being a significant prognostic marker, HRV provide at least some information regarding the overall functioning of the cANS. The near-normal resting HRV index values observed in implanted and explanted patients suggest a degree of autonomic normalisation. It appears that by unloading the left ventricle, the cycle of sympathetic over activity is corrected to a significant degree. These data show that LVAD therapy potentially restores predictable responses and near normal values for reflex cardiac autonomic activity in the cANS of what were once most-likely severely deranged systems of patients with end stage heart failure.

5. Limitations

We acknowledge that the major limitation of this study is the cross-sectional design. During the study period, only one patient with end-stage heart failure was implanted then explanted from LVAD. Moreover, only two patients moved from implanted to explanted states. The duration of a study required to collect longitudinal data would appear to be more than several years. Of note is that the thirty-seven patients in the present study represent a very large proportion of survivors of LVAD implantation (and explantation) over a period of approximately five years. In fact, they represented the entire ongoing LVAD implant population from our hospital that at the time of the study were in sinus rhythm and/or not paced. In turn, they also

represent a very large proportion of the total UK LVAD population. Only three patients were not able to have HRV measured. In one case this was due to persistent atrial fibrillation and two other cases due to the use of implantable pacing devices.

We recommended that a longitudinal study, tracking changes in HRV and possibly baroreflex gain or other sympathetic measurement be carried out to determine if LVAD therapy can lead to definite autonomic recovery in successfully treated patients. A single-centre prospective study may be prohibitively long or may have very small subject numbers. Such data collection would no doubt be made easier by collaboration and co-operation between units in order to combine their experience and data to provide a better overall understanding of the outcomes from this rare but seemingly very successful intervention.

6. Conclusions

Patients implanted with and explanted from a LVAD following myocardial recovery demonstrate a lower HRV risk profile compared to patients with end-stage heart failure and have a dynamic response to autonomic stimuli similar to healthy matched controls.

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