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Sympathetic Markers Differentiate Health-Related Quality of Life Clinical Responders and Non-Responders Following Left Ventricular Assist Device Implantation

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Abstract

Background: Clinical response to left ventricular assist devices (LVAD), as measured by health-related quality of life (HRQOL), varies among patients following implantation; however, it is unknown which pathophysiological mechanisms underlie differences in clinical response by HRQOL.

Objective: The purpose of this study was to compare changes in sympathetic markers (β -adrenergic receptor kinase-1 (β ARK1), norepinephrine (NE), and 3,4-dihydroxyphenylglycol (DHPG)) between HRQOL clinical responders and non-responders from pre- to post-LVAD.

Methods—We performed a secondary analysis on a subset of data from a cohort study of patients from pre- to 1, 3, and 6 months post-LVAD. Clinical response was defined as ≥ 5 points increase on the Kansas City Cardiomyopathy Questionnaire Clinical Summary score from pre- to 6-months post-LVAD. We measured plasma β ARK1 with an ELISA and plasma NE and DHPG with high performance liquid chromatography with electrochemical detection. Latent growth curve modeling was used to compare trajectories of markers between groups.

Results: Average age of the sample ($n=39$) was 52.9 ± 13.2 years, and most were male (74.4%) and bridge to transplant (69.2%). Pre-implant plasma β ARK1 was significantly higher in clinical responders ($n=19$) vs. non-responders ($n=20$) ($p=0.001$), but change was similar following LVAD ($p=0.235$). Pre-implant plasma DHPG was significantly lower in clinical responders vs. non-

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responders ($p=0.002$), but change was similar following LVAD ($p=0.881$). There were no significant differences in plasma NE.

Conclusions: Pre-implant β ARK1 and DHPG levels are differentiating factors between HRQOL clinical responders and non-responders to LVAD, potentially signaling differing levels of sympathetic stimulation underlying clinical response.

Introduction

With the rise in the number of left ventricular assist devices (LVAD) as therapy for advanced heart failure (HF) patients,¹ there is a need to assess the clinical response following implantation. The traditional paradigm of clinical response is driven by improvements in survival and a reduction in adverse clinical events.² In recent years, there has been a drive to understand clinical response using patient-reported outcome metrics such as health-related quality of life (HRQOL) in cardiovascular clinical trials,³ particularly among LVAD patients.⁴ Measuring patient-reported outcomes is critical because HRQOL can vary drastically among HF patients post-LVAD implantation, and importantly, not all patients have improved HRQOL after LVAD.^{5,6} HRQOL is a complex phenomenon that encompasses clinically relevant aspects of life related to physical and mental health dimensions.⁷ While HRQOL is largely influenced by symptoms, treatment effects, social well-being, and functionality,⁸ particularly in HF,⁹ there is also a need to understand variability in HRQOL as a function of biological and physiological mechanisms. Understanding the biological and physiological mechanisms of HRQOL is particularly important among patients receiving a LVAD given the drastic physiologic changes that occur post-implantation. In turn, this understanding could help identify who will have better or worse HRQOL following LVAD implantation.

Underlying differences in HRQOL could involve pathophysiological mechanisms such as the sympathetic nervous system, which is chronically activated in HF and leads to the deterioration of left ventricular function, remodeling, and worsening symptoms.¹⁰ One method to assess sympathetic activity involves measuring biomarkers such as plasma β -adrenergic receptor kinase-1 (β ARK1; a.k.a. G protein-coupled receptor kinase-2) and plasma catecholamines, specifically norepinephrine (NE). Increases in both plasma β ARK1 and NE signal sympathetic over activation. Specifically, β ARK1 causes desensitization and internalization of β -adrenergic receptors following augmented and chronic stimulation by NE.¹¹ Expression of β ARK1 in myocardial cells and lymphocytes has been linked with prognosis in HF¹² and has been shown to decrease following LVAD implantation¹³ and heart transplantation.¹⁴ Recently, we showed that elevated plasma β ARK1 is associated with worse physical HF symptoms.¹⁵ Additionally, plasma NE is commonly used as an index of sympathetic activity, and elevated plasma NE is associated with poor left ventricular function and mortality in HF.¹⁶ Concurrently measuring the principal metabolite of NE, 3,4-dihydroxyphenylglycol (DHPG), also provides insight into NE dynamics; specifically, the ratio of NE:DHPG helps to discern whether increased NE is caused by sympathetic over activation or blunted NE reuptake.¹⁷⁻¹⁹

The purpose of this study was to compare changes in plasma β ARK1, NE, and DHPG between HRQOL clinical responders and non-responders from pre- to post-LVAD implantation. We hypothesized that clinical responders would have greater reductions in plasma β ARK1, NE, and DHPG from pre- to post-LVAD implantation compared with non-responders.

Methods

Study Design

This was a secondary analysis of a subset (n=39) of biorepository data and plasma samples collected as part of a U.S. National Institutes of Health-funded cohort study examining biobehavioral responses following continuous flow LVAD placement (n=101).^{20,21} Given limited resources, we were only able to measure sympathetic markers in a subset of plasma samples from the parent study. In the parent study, data and plasma samples were collected at baseline or pre-LVAD implantation (median of 4 days pre-implant) and at 1, 3, and 6 months post-LVAD implantation. Key inclusion criteria for the parent study were age 21 years or older, ability to read and comprehend 5th grade English or Spanish, and eligibility for implantation of a commercially available, U.S. Food and Drug Administration-approved continuous flow LVAD as a bridge to transplantation/decision or as destination therapy. Potential participants were excluded if they had documented major cognitive impairment (e.g. Alzheimer's disease), major psychiatric illness, prior heart transplantation or mechanical circulatory support, or if they had a concomitant terminal illness that impeded participation in a 6-month study. The participants were recruited through a single center in the Pacific Northwest between April 2012 and May 2016. Our Institutional Review Board approved both this study and the parent study; written informed consent was obtained from all participants for the parent study and to have their data and samples stored in a de-identified biorepository for future research.

Measurement

Sample of clinical responders and non-responders.—To detect differences in sympathetic markers between clinical responders and non-responders, we selected a subset of patients (n=39) from the larger parent study who either had distinct clinical response from pre- to post-LVAD implantation (n=19) or had distinct clinical non-response (n=20). In the absence of a clear definition of clinical response to LVAD by HRQOL, we based our definition of response on clinically meaningful improvements on the Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score.^{22,23} The KCCQ is a HF-specific measure of health status used to quantify physical limitation, symptoms, quality of life, social limitation, and self-efficacy.²³ For the purposes of this study, and to focus on HRQOL, we used the Clinical Summary Score, which is a composite of the physical limitation, symptom, quality of life, and social limitation domains. Scores range from 0 to 100 with higher scores reflecting better HRQOL. Clinical response was defined by ≥ 5 points increase on the KCCQ Clinical Summary score between pre- and 6 months post-LVAD. Clinical non-response was defined by < 5 points increase or decrease on the KCCQ Clinical Summary score between pre- and 6 months post-LVAD and/or an average < 45 across the 1, 3, and 6 months post-implant time points.^{6,22}

Sociodemographic and clinical data.—Baseline data on age, gender, marital status, race, and education were obtained using a sociodemographic questionnaire. Baseline data on history, etiology, and treatment of HF, as well as New York Heart Association functional class, were collected through an in-depth review of the electronic medical record. Data were also collected on baseline clinical and laboratory characteristics, including parameters from echocardiographic assessments and from right heart catheterization procedures. Comorbid conditions were summarized using the Charlson Comorbidity Index.²⁴ Post-implantation treatment characteristics and events (infection, neurologic event, and hemorrhagic event) were recorded at 1, 3, and 6 months post-LVAD.

Plasma sympathetic markers.—Whole blood was collected from participants and centrifuged at 2800 rpm for 10 minutes at 5°C to separate plasma, which was stored at −80°C. When ready to process, frozen plasma samples were thawed and centrifuged. We used a commercially available ELISA (Cusabio, College Park, MD) to quantify plasma β ARK1 based on a quantitative sandwich immunoassay technique according to manufacturer's instructions. We ran samples in duplicate in parallel with a standard curve composed of known β ARK1 concentrations (18.75–1200 pg/mL). After subtracting the blank readings and log transforming the concentrations, we used a sigmoidal four-parameter logistic curve to quantify β ARK1 in each of the samples as interpolated from the standard curve; mean values of the duplicates were reported. The potential range for plasma β ARK1 was 0–1200 pg/mL, but there is no identified cut point to indicate healthy levels. The average intra-assay coefficient of variation was 10.5%, and the inter-assay coefficient of variation was 21.2%.

We used high performance liquid chromatography with electrochemical detection (HPLC-ED) to measure the plasma catechols, NE and DHPG, as previously described.²⁵ Briefly, the internal standard, dihydroxybenzylamine, was added to plasma samples and to standards, and the catechols were pre-purified by alumina extraction. The catechols were separated by reversed-phase chromatography on C18 column (Agilent Microsorb, 150×4.6 mm, 5 μ m) using a filtered and degassed mobile phase (75 mM sodium phosphate (pH 3.0), 1.7 mM sodium octane sulfonate, 1.5% acetonitrile). An electrochemical detector (Coulchem III; ESA, Bedford, MA) was used to detect and quantify the catechols. We adopted an oxidation-reduction protocol (electrodes set to +300 mV, +150mV, and −350 mV based on previous research²⁶) to eliminate a contaminating peak of uric acid that co-eluted with DHPG. Uric acid was undetectable and recoveries of both NE and DHPG in the plasma samples were adequate using this method.²⁵ The potential range of plasma NE is dependent on the assay method, but generally averages about 0.5–3 pmol/mL;^{18,27} plasma DHPG is about 5–6 times higher than plasma NE.¹⁸ In each of the assays, we also included samples of de-identified pooled plasma stored from healthy volunteers as a comparison. The average intra-assay coefficient of variation was 5.3%, and the inter-assay coefficient of variation was 4.6%.

Statistical Analysis

Standard descriptive statistics of frequency, central tendency, and dispersion were used to describe the sample. Raw values of plasma β ARK1, NE, and DHPG were natural log-transformed to approximate normality; both raw values and log-transformed values were

used in analyses. We used traditional comparative statistics (i.e. Student's t , Mann-Whitney U, Fisher's exact, or the Pearson's chi-square tests) to compare differences in clinical characteristics between clinical responders and non-responders at baseline and differences in KCCQ Clinical Summary Scores, log β ARK1, logNE, logDHPG, and logNE:logDHPG ratio at each time point. The Pearson's chi-square test (or Fisher's exact tests with small cell sizes) were used to compare treatment and event rate characteristics between clinical responders and non-responders post-implantation.

We used latent growth curve modeling to quantify trajectories in raw values of the sympathetic markers (i.e. β ARK1, NE, and DHPG, and the ratio of NE:DHPG) between clinical responders and non-responders. Latent growth curve modeling allows for the estimation of inter-individual variability in intra-individual patterns of change using latent intercepts (i.e. the pre-implantation values) and latent slopes (i.e. rate of change over 6 months).²⁸ While originally developed in the social sciences, latent growth curve modeling has been applied to other areas such as the study of biomarkers.²⁹ It is particularly robust in situations with missing data, unequally spaced time points, non-linear trajectories, and non-normally distributed repeated measures. In our analysis, we used a known group growth model to compare changes in sympathetic markers (i.e. mean intercepts and mean slopes) between clinical responders and non-responders. KCCQ Clinical Summary scores were available for the patients at every time point; however, plasma samples were not available for 5 participants at the 6-month time point. Full information maximum likelihood estimation was used to handle these missing data for the trajectories. Significance was set at $\alpha < 0.05$. With a minimum sample size of 38 (19 in each group) and an α of 0.05, we were powered at 0.80 to detect a Cohen's $d > 0.95$ (large effect size) using a Student's t test between clinical responders and non-responders. GraphPad Prism 7.0 (San Diego, CA) was used to interpolate the β ARK1 levels based on standard curves and to prepare the figures. All other analyses were performed using Stata/MP v.15 (College Station, TX) and MPlus v.8 (Los Angeles, CA).

Results

The young, mostly male sample had primarily non-ischemic HF etiology (primarily idiopathic dilated cardiomyopathy), and most were implanted as a bridge to transplant (Table 1). The sample had, on average, between 2 and 3 comorbidities, and about half the sample had concurrent atrial fibrillation. Patients had, on average, high filling pressures and low ejection fractions, and the majority were treated with evidence-based therapies at baseline. There were significant differences in body mass index and plasma N-terminal pro-B-type natriuretic peptide between clinical responders and non-responders, and more clinical responders had pre-operative intra-aortic balloon pump support; otherwise the remaining clinical characteristics were similar between groups at baseline.

Post-implantation, there were no significant differences in treatment characteristics or event rates. By 6 months post-implantation, 73.7% of clinical responders and 70.0% of non-responders were being treated with a beta-blocker ($\chi^2 = 0.07$, Fisher's exact $p = 1.00$), and 84.2% of clinical responders and 65.0% of non-responders were being treated with either an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker ($\chi^2 = 1.89$, Fisher's

exact $p = 0.27$). There were no deaths in either group post-implantation. By 6 months post-implantation, there were no significant differences between clinical responders and non-responders in infection rates (26.3% versus 40.0%; $\chi^2 = 0.82$, Fisher's exact $p = 0.50$), neurological events (5.3% versus 10.0%; $\chi^2 = 0.31$, Fisher's exact $p = 1.00$), or hemorrhagic events (15.8% versus 20.0%, $\chi^2 = 0.12$, Fisher's exact $p = 1.00$).

Clinical responders had significantly lower KCCQ Clinical Summary Scores at baseline compared with non-responders (40.3 ± 16.5 vs. 62.6 ± 19.9 , $p < 0.001$). Because of our study design, clinical responders had significantly higher KCCQ Clinical Summary Scores at 1 months (73.8 ± 19.0 vs. 48.4 ± 21.1 , $p < 0.001$), 3 months (81.7 ± 12.5 vs. 62.7 ± 15.8 , $p < 0.001$), and 6 months (83.0 ± 13.9 vs. 57.4 ± 15.7 , $p < 0.001$) post-LVAD compared with non-responders. In latent growth curve modeling, the change (slope) in scores were also significantly different between the groups (Figure 1).

Clinical responders had significantly lower plasma $\log\beta\text{ARK1}$ levels compared with clinical non-responders at the pre-implant ($p = 0.001$) and 6 months post-LVAD ($p = 0.01$) time points (Table 2). In latent growth curve modeling, we found that pre-implant plasma βARK1 (intercept) was significantly lower in clinical responders compared with non-responders ($z = -3.201$, $p = 0.001$), but change (slope) in plasma βARK1 over time was not significantly different between the groups ($z = -1.187$, $p = 0.235$) (Figure 2).

There were no significant differences in plasma $\log\text{NE}$ between clinical responders and non-responders at any of the time points (Table 2), and the latent growth curve modeling intercepts ($z = 0.895$, $p = 0.371$) and slopes of changes ($z = -0.861$, $p = 0.389$) were not significantly different (Figure 3A). There were, however, significant differences in plasma $\log\text{DHPG}$ levels at pre-implant ($p = 0.003$), 1 month post-LVAD ($p = 0.003$), and 6 months post-LVAD ($p = 0.01$) (Table 2). In latent growth curve modeling, we found that pre-implant plasma DHPG (intercept) was significantly higher in clinical responders compared with non-responders ($z = 3.149$, $p = 0.002$), but change (slope) in plasma DHPG over time was not significantly different between the groups ($z = 0.150$, $p = 0.881$) (Figure 3B). Interestingly, the DHPG levels in the clinical responders were closer to our healthy plasma comparison. There were no significant differences in plasma $\log\text{NE}:\log\text{DHPG}$ ratio between clinical responders and non-responders at any of the time points (Table 2), and the latent growth curve modeling intercepts ($z = -1.000$, $p = 0.317$) and slopes of change ($z = -1.496$, $p = 0.135$) were not significantly different (Figure 3C). The NE:DHPG ratio for clinical responders, however, more closely approximated the healthy plasma NE:DHPG ratio compared with the non-responders (Figure 3C).

Discussion

The purpose of this study was to examine changes in sympathetic markers in relation to clinical response following LVAD implantation, based on a HRQOL metric, as a way to begin pinpointing pathophysiological processes underlying better or worse response after LVAD. Our key findings were 1) clinical responders have significantly lower pre-implant plasma βARK1 and higher plasma DHPG (the primary metabolite of NE) compared with non-responders to LVAD and 2) the differences in plasma βARK1 and DHPG between

clinical responders and non-responders at pre-implant are maintained through 6 months post-LVAD implantation. These differences potentially signal differing levels of sympathetic activation in relation to clinical response that can be identified at pre-implantation.

There was a clear differentiation in the trajectories of plasma β ARK1 levels between clinical responders and non-responders, which is in line with our previous work that showed higher plasma β ARK1 levels are associated with worse physical HF symptoms.¹⁵ Among clinical responders to LVAD, β ARK1 levels started low and remained low through 6 months post-LVAD. On the other hand, among clinical non-responders to LVAD, β ARK1 levels started high and remained high through 6 months post-LVAD. This finding indicates that the pre-implant β ARK1 level may be the most informative data point in predicting who will have a better clinical response. In other words, if the β ARK1 level is low pre-implant, then it will likely remain low through 6 months post-LVAD and, without considering other variables, could be associated with improved HRQOL.

The significant differences in plasma DHPG levels between clinical responders and non-responders, coupled with non-significant differences in plasma NE levels, could indicate blunted NE reuptake, as previously noted by Eisenhofer et al.¹⁸ Notably, even though clinical responders had higher plasma DHPG levels at every time point, their levels more closely approximated our healthy plasma reference line. Additionally, the ratio of NE:DHPG in clinical responders was closer to the ratio of NE:DHPG observed in healthy plasma compared with non-responders, although the difference in trajectories was not statistically significant. Since DHPG arises from deamination of NE by monoamine oxidase, we can use the ratio to identify whether there is increased sympathetic stimulation (NE:DHPG ratio remains constant) or whether there are problems with NE reuptake (NE:DHPG ratio increases).¹⁹ If similar results are found in larger prospective studies, the ratio of NE:DHPG could be helpful in identifying the lack of NE reuptake as underlying poor clinical response.

Clinically speaking, , higher plasma β ARK1 levels, lower plasma DHPG levels, and higher NE:DHPG ratios may signal chronic sympathetic dysregulation in this group of clinical non-responders compared with a group of clinical responders. Despite being on similar therapies at baseline, the clinical non-responders have a significantly different sympathetic profile, compared with the clinical responders, and the difference in sympathetic profiles did not change with LVAD implantation. These findings indicate that this group of clinical non-responders, who had poor HRQOL post-LVAD, also had a higher level of sympathetic over activation and dysregulation, which was not mitigated post-LVAD. Given these preliminary signals, it would be worthwhile to explore sympathetic dysregulation, in part, as underlying patient-reported outcomes, including symptoms and HRQOL.³⁰

Chronic sympathetic stimulation is a hallmark of HF pathophysiology and a target for HF therapies such as beta-blockade.¹⁰ However, the exact mechanisms for the sympathetic changes that occur after implantation of a continuous flow LVAD are unclear, particularly given the loss of pulsatility that could affect baroreceptor unloading.³¹ Markham et al. showed that patients with non-pulsatile LVADs had higher muscle sympathetic nerve activity than patients with pulsatile LVADs despite similar hemodynamic and medical therapy profiles.³² Grosman-Rimon et al. recently demonstrated that NE levels remain elevated after

implantation of a continuous flow LVAD and are similar to HF controls.²⁷ We have taken this one-step further and showed that while over activation of the sympathetic nervous system persists post-LVAD, there is a different sympathetic profile between clinical responders and non-responders, using a patient-reported outcome metric. Our findings show that there is a graded difference in sympathetic dysregulation, which may help to pinpoint one potential mechanism underlying stagnantly poor HRQOL post-LVAD.

There are a few noted limitations to this study. First, this was a small sample of clinical responders and non-responders, and we were likely underpowered to detect some significant differences. Despite the small sample size, however, our analysis identified a signal of two sympathetic biomarkers that track with HRQOL among LVAD patients and can provide a starting point for further research. Moreover, the small sample size precluded the inclusion of time-varying covariates such as plasma N-terminal pro-B-type natriuretic peptide. Future research should account for other factors that may influence pre- and post-LVAD HRQOL and sympathetic markers, including the Interagency Registry for Mechanically Assisted Circulatory Support score and implant strategy. Second, this sample was comprised of mostly male Non-Hispanic Caucasians with a non-ischemic HF etiology from one advanced HF clinic in the Pacific Northwest. Given the known gender and racial differences in HF etiology, presentation, and patient-reported outcomes, these findings may not be generalizable to the advanced HF population at large. Third, it is important to note that regulation of sympathetic activity is complex, and we did not assess other inputs to sympathetic activation. Future research should examine other techniques to assess sympathetic activity (e.g. measuring norepinephrine kinetics³³ or microneurography³⁴). Finally, while the KCCQ has been well-validated and used extensively among HF patients in general, there is no gold standard measure to assess HRQOL in LVAD patients, a group of patients with unique concerns and burdens.³⁵

In addition, future research should prospectively investigate changes in these and other sympathetic markers in a larger cohort of advanced HF patients receiving a LVAD. If future work supports the finding that sympathetic markers underlie differing HRQOL trajectories, it may be possible to identify clinical interventions that target sympathetic over activation (e.g. pharmacological, exercise, and/or self-care interventions^{10,36,37}) as a means to improve HRQOL post-LVAD. Additionally, future research should focus on identifying and building a multi-marker profile that will further differentiate those who are likely to have poor HRQOL post-LVAD. Specifically, future work should examine the role of traditional markers like N-terminal pro-B-type natriuretic peptide along with novel markers in predicting better or worse response. Finally, clinical responders in this sample had significantly lower HRQOL pre-implantation and therefore had more room for improvement post-implantation compared with clinical non-responders; as such, future research should dissect apart the reason certain groups of patients start at varying degrees of HRQOL pre-implantation.

Conclusions

In this study, we provided preliminary evidence that sympathetic markers differentiate HRQOL clinical responders compared with non-responders following continuous flow

LVAD implantation. With the movement towards understanding changes in patient-reported outcomes comes the need to understand the biological mechanisms underlying these patient-reported outcomes. These findings help lay the foundation towards improving patient-reported outcomes for patients undergoing LVAD implantation.

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Figure 1. Trajectories of health-related quality of life in clinical responders and non-responders to LVAD.

Clinical response was defined by improvements in HRQOL, as measured with the KCCQ Clinical Summary Score, from pre-LVAD to 6 months post-LVAD (shown as mean $\pm$ SEM).

In latent growth curve modeling, the intercept (or pre-implant) score was not significantly different between clinical responders (solid line; $n = 19$) and non-responders (dashed line; $n = 20$) ($z = -0.239$; $p = 0.811$), but the slope of change was significantly different ($z = 3.840$; $p < 0.001$). *Abbreviations: HRQOL, health-related quality of life; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVAD, left ventricular assist device; SEM, standard error of the mean.*

Figure 2. Trajectories of plasma β ARK1 in clinical responders and non-responders to LVAD. Plasma β ARK1 levels (shown as mean $\pm$ SEM) were measured in clinical responders (solid line; $n = 19$) and non-responders (dashed line; $n = 20$) from pre- to 6 months post-LVAD. In latent growth curve modeling, the intercept (or pre-implant) plasma β ARK1 was significantly different between clinical responders and non-responders ($z = -3.201$, $p = 0.001$), but the slope of change was not significantly different ($z = -1.187$, $p = 0.235$). *Abbreviations: β ARK1, β -adrenergic receptor kinase-1; LVAD, left ventricular assist device; SEM, standard error of the mean.*

Figure 3. Trajectories of plasma NE, DHPG, and NE:DHPG ratio in clinical responders and non-responders to LVAD.

Plasma NE (A) and DHPG levels (B) and NE:DHPG ratio (C) (shown as mean $\pm$ SEM) were measured in clinical responders (solid line; $n = 19$) and non-responders (dashed line; $n = 20$) from pre- to 6 months post-LVAD. The healthy plasma level for each marker was included as a reference line in each panel. In latent growth curve modeling, the intercept (or pre-implant) plasma DHPG was significantly different between clinical responders and non-responders ($z = 3.149$, $p = 0.002$), but the slope of change was not significantly different ($z = 0.150$, $p = 0.881$). There were no significant differences in trajectories of plasma NE (intercept: $z = 0.895$, $p = 0.371$; slope: $z = -0.861$, $p = 0.389$) or the NE:DHPG ratio (intercept: $z = -1.000$, $p = 0.317$; slope: $z = -1.496$, $p = 0.135$) between clinical responders and non-responders. *Abbreviations: DHPG, 3,4-dihydroxyphenylglycol; NE, norepinephrine; LVAD, left ventricular assist device; SEM, standard error of the mean.*

Table 1:
Characteristics of the Sample at Baseline (Pre-Implantation)

	M±SD, N(%), or Median [IQR]		
	Clinical Responders (n=19)	Clinical Non-Responders (n=20)	p value
Patient Characteristics:			
Age (years)	56.5±12.6	49.4±13.1	0.092
Male	14 (73.7)	15 (75)	0.925
Non-Hispanic Caucasian	17 (89.5)	15 (75)	0.407
Education level			
High school or less	5 (26.3)	9 (45.0)	0.310
>High school but < college	9 (47.4)	9 (45.0)	
College degree	5 (26.3)	2 (10.0)	
Body mass index (kg/m ²)	26.4±3.9	31.1±6.2	0.008
Charlson Comorbidity Index (weighted)	2.2±1.2	3.0±1.6	0.090
Atrial fibrillation	10 (52.6)	12 (60.0)	0.643
General Heart Failure Characteristics:			
Time with heart failure (years)	4.3 [0.33–11.0]	6.5 [1.5–14.1]	0.633
NYHA functional class			
Class II	1 (5.3)	1 (5.0)	0.247
Class III	6 (31.6)	12 (60.0)	
Class IV	11 (57.9)	7 (35.0)	
Non-ischemic etiology	13 (68.4)	12 (60.0)	0.584
Prescribed a β-blocker	6 (31.6)	10 (50.0)	0.242
Prescribed an ACE-I or ARB	14 (73.7)	16 (80.0)	0.716
Inotropic support	13 (68.4)	14 (70.0)	0.915
Intra-aortic balloon pump	11 (57.9)	4 (40.0)	0.022
Serum sodium (mEq/L)	133.7±3.9	133.9±3.7	0.861
Serum hematocrit (%)	35.9±6.3	34.8±4.3	0.547
Serum BUN/creatinine ratio (mg/dL:1)	23.5 [18.5–26.5]	18.1 [13.9–23.8]	0.068
Left ventricular internal end-diastolic diameter (cm)	7.2±1.3	7.4±1.2	0.651
Left ventricular ejection fraction (%)	20.0±0.0	20.4±1.2	0.202
Pulmonary capillary wedge pressure (mm/Hg)	22.9±8.3	21.4±6.9	0.530
Right atrial pressure (mm/Hg)	9.6±3.7	8.0±4.4	0.204
Cardiac index (L/min/m ² by Fick equation)	2.0±0.7	1.9±0.4	0.537
Plasma NT-proBNP (pg/mL)	4079 [2481–6496]	2305 [1017.5–3734]	0.011
LVAD Characteristics			
INTERMACS Category			
1	1 (5.3)	1 (5.6)*	0.728
2/3	14 (73.7)	11 (61.1)	
4/5	4 (21.1)	6 (33.3)	
Implant strategy			

M±SD, N(%), or Median [IQR]			
	Clinical Responders (n=19)	Clinical Non-Responders (n=20)	p value
Bridge to transplantation	13 (68.4)	14 (70.0)	1.000
Bridge to decision	1 (5.3)	2 (10.0)	
Destination therapy	5 (26.3)	4 (40.0)	
Device			
Heartmate II	14 (73.7)	13 (65.0)	1.000
Heartware	5 (26.3)	6 (30.0)	
Heartmate III	0 (0.0)	1 (5.0)	

* data not available for 2 non-responders

Abbreviations: ACE-I, Angiotensin Converting Enzyme-Inhibitor; ARB, Angiotensin Receptor Blocker; β ARK1, β -adrenergic receptor kinase-1; BUN, blood urea nitrogen; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; IQR, interquartile range; LVAD, left ventricular assist device; M, mean; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation

Table 2:

Comparison of Sympathetic Markers between Health-Related Quality of Life Clinical Responders ($n = 19$) and Non-Responders ($n = 20$) Pre- to Post-Left Ventricular Assist Device Implantation

	Mean±SD			
	Pre-LVAD	1 mo. Post-LVAD	3 mo. Post-LVAD	6 mo. Post-LVAD
log β ARK1				
Responders	2.1±2.0	3.4±1.2	3.0±1.5	2.8±1.7
Non-Responders	4.1±1.6	4.1±1.7	3.9±1.9	4.5±1.7
	$p = 0.001$	$p = 0.12$	$p = 0.10$	$p = 0.01$
logNE				
Responders	1.9±0.7	1.6±0.6	1.6±0.6	1.6±0.5
Non-Responders	1.6±0.6	1.6±0.6	1.6±0.6	1.5±0.7
	$p = 0.17$	$p = 0.79$	$p = 0.99$	$p = 0.55$
logDHPG				
Responders	3.1±0.4	2.8±0.3	2.6±0.4	2.6±0.4
Non-Responders	2.6±0.5	2.5±0.3	2.4±0.3	2.2±0.5
	$p = 0.003$	$p = 0.003$	$p = 0.10$	$p = 0.01$
logNE:logDHPG Ratio				
Responders	0.6±0.2	0.6±0.2	0.6±0.2	0.6±0.2
Non-Responders	0.6±0.3	0.6±0.2	0.7±0.3	0.7±0.4
	$p = 0.85$	$p = 0.41$	$p = 0.43$	$p = 0.34$

Abbreviations: log β ARK1, natural log of β -adrenergic receptor kinase-1; logDHPG, natural log of dihydroxyphenylglycol; logNE, natural log of norepinephrine; SD, standard deviation.