Hypotension on cardiopulmonary stress test predicts 90 day mortality after LVAD implantation in INTERMACS 3–6 patients

Valmiki Maharaj¹, Arianne C. Agdamag¹, Sue Duval¹, Jonathan Edmiston², Victoria Charpentier³, Meg Fraser¹, Alexandra Hall², Jessica Schultz¹, Ranjit John⁴, Andrew Shaffer⁴, Cindy M. Martin¹, Thenappan Thenappan¹, Gary S. Francis¹, Rebecca Cogswell¹ and Tamas Alexy¹*

¹Department of Medicine, Division of Cardiology, University of Minnesota, Minneapolis, MN, USA; ²Department of Medicine, University of Minnesota, Minneapolis, MN, USA; ³University of Minnesota Medical School, Minneapolis, MN, USA; and ⁴Division of Cardiothoracic Surgery, Department of Surgery, University of Minnesota, Minneapolis, MN, USA

Abstract

Aims Cardiopulmonary stress test (CPX) is routinely performed when evaluating patient candidacy for left ventricular assist device (LVAD) implantation. The predictive value of hypotensive systolic blood pressure (SBP) response during CPX on clinical outcomes is unknown. This study aims to determine the effect of hypotensive SBP response during to clinical outcomes among patients who underwent LVAD implantation.

Methods and results This was a retrospective single center study enrolling consecutive patients implanted with a continuous flow LVAD between 2011 and 2022. Hypotensive SBP response was defined as peak exercise SBP below the resting value. Multivariable Cox-regression analysis was performed to evaluate the relationship between hypotensive SBP response and all-cause mortality within 30 and 90 days of LVAD implantation. A subgroup analysis was performed for patients implanted with a HeartMate III (HM III) device. Four hundred thirty-two patients underwent LVAD implantation during the pre-defined period and 156 with INTERMACS profiles 3–6 met our inclusion criteria. The median age was 63 years (IQR 54–69), and 52% had ischaemic cardiomyopathy. Hypotensive SBP response was present in 35% of patients and was associated with increased 90 day all-cause mortality (unadjusted HR 9.16, 95% CI 1.98–42; P = 0.0046). Hazard ratio remained significant after adjusting for age, INTERMACS profile, serum creatinine, and total bilirubin. Findings were similar in the HM III subgroup.

Conclusions Hypotensive SBP response on pre-LVAD CPX is associated with increased perioperative and 90 day mortality after LVAD implantation. Additional studies are needed to determine the mechanism of increased mortality observed.

Keywords Cardiopulmonary exercise stress test; Left ventricular assist device; Hypotension; Heart failure

Introduction

Cardiopulmonary exercise stress test (CPX) is a versatile tool that enables the objective, non-invasive, and global performance assessment of the cardiopulmonary system at rest and during exercise. It was primarily used for research purposes initially, but became increasingly available to clinicians as it evolved in technology and scope.¹ CPX is now routinely used as a diagnostic modality in the evaluation of patients with dyspnoea, exercise intolerance, and to objectively determine functional capacity. It was also added to the heart failure (HF) cardiologist’s tool box after Weber and colleagues introduced a peak oxygen consumption (VO₂max)-based classification system for patients with heart failure with reduced ejection fraction (HFrEF).² In a subsequent seminal paper, VO₂max was shown to predict 1-year cardiovascular mortality in a population with advanced HF.³ The combined use of measured and calculated CPX parameters became the stan-
Hypertension on CPX and outcomes after LVA

3497

standard in the early 2000s and this multivariable approach is now integrated into the routine algorithms utilized when establishing heart transplant candidacy.5–6

With limited donor heart availability and advancements in technology, left ventricular assist devices (LVADs) are increasingly utilized in the management of patients with advanced HF. LVAD therapy improves life expectancy, quality of life, and functional capacity when compared with medical therapy alone.7,8 Although CPX is often performed prior to LVAD implantation, data evaluating the relationship between measures of exercise performance and outcomes in this population are scarce.

Systolic blood pressure (SBP) response to exercise depends on multiple factors such as age, ethnicity, sex, and physical fitness. Generally, it is expected to rise along with increasing workloads.9 The lack of increase or a drop in SBP with exercise has been associated with adverse long-term outcomes, such as increased all-cause mortality and incident myocardial infarction.10–14 Similarly, chronotropic incompetence during treadmill stress test is noted to be a predictor of mortality.15 However, the predictive value of hypotensive response during exercise on outcomes after LVAD surgery remains unknown. Therefore, the purpose of this study was to evaluate the prognostic implications of hypotensive SBP response during CPX study on clinical outcomes following LVAD implantation.

Methods

Study cohort

The Institutional Review Board of the University of Minnesota approved this study. We retrospectively reviewed the charts of 432 consecutive patients who underwent continuous flow LVAD implantation at our centre between January 2011 and March 2022. All patients who completed a CPX study using the Naughton protocol within 1 year prior to LVAD surgery were included. Exclusion criteria included (i) lack of CPX within 1 year before LVAD surgery; (ii) Interagency Registry for Mechanical Circulatory Support (INTERMACS) 1 and 2 profile at the time of LVAD implantation; (iii) LVAD exchange; (iv) need for durable biventricular mechanical circulatory support; (v) congenital heart disease. The following demographic and clinical variables were collected at the time of surgery: age, sex, body mass index (BMI), aetiology of cardiomyopathy (ischaemic vs. non-ischaemic), serum creatinine, serum albumin, total bilirubin, NT-pro-B-type natriuretic peptide (NT-proBNP) level, history of systemic arterial hypertension, presence of diabetes mellitus, and INTERMACS profile. Outcomes assessed during the immediate post-operative period included intensive care unit (ICU) and total hospital length of stay, duration of mechanical ventilation, vasoactive medications, and pulmonary vasodilator use. Pulmonary vasodilators included prostacyclin and phosphodiesterase-5 (PDE-5) inhibitors. In addition, the outcomes of liver failure, need for dialysis, right ventricular assist device placement, or cerebrovascular accident within 90 days of LVAD implantation were recorded. Liver failure was defined as serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels exceeding five times the upper limit of normal or total bilirubin higher than 5 mg/dL. Cerebrovascular accident was defined as a neurological deficit of cerebrovascular cause that persisted beyond 24 h or led to patient death within 24 h. Lastly, vital status and number of readmissions within 90 days of implantation were recorded. Any overnight hospital stay within the first 90 days of LVAD surgery was considered a readmission. Follow-up was censored at the time of cardiac transplantation. In addition to the full cohort, a pre-defined subgroup analysis limited to patients undergoing HeartMate III (HM III, Abbott Laboratories, Minneapolis, MN, USA) device implantation was also performed.

Evaluative parameters on cardiopulmonary stress test

The following parameters obtained during the routine CPX study were reviewed and recorded: exercise duration, peak metabolic equivalent (MET), BP at rest and at peak exercise, and the presence of hemodynamically significant arrhythmia on electrocardiogram (ECG). Data on complete breath-to-breath gas analysis were also recorded and analysed for all patients, including $V_{O2}$max, carbon dioxide production ($VCO_2$), minute ventilation ($V_t$), ventilatory equivalent of carbon dioxide ($V_t/VCO_2$), and respiratory exchange ratio (RER).

Primary predictor and clinical outcomes

The primary predictor for this analysis was SBP response during the pre-LVAD CPX and the primary outcome was all-cause mortality within 90 days of LVAD implantation. Patients were stratified into categories based on SBP response: (i) hypotensive, defined as a peak exercise SBP lower than the value recorded at rest, and (ii) normal response.

Statistical methods

Descriptive statistics are reported as mean and standard deviation (SD) for normally distributed variables, or median and interquartile range (IQR) for nonnormally distributed variables. Categorical variables are presented as frequencies and percentages. Tables were generated comparing those with hypotensive response to those who had normal blood pressure response on CPX. Normally distributed continuous variables were compared with unpaired t-tests and Wilcoxon
rank sum tests were used for non-normally distributed continuous variables. Categorical variables were compared using Pearson $\chi^2$ or Fisher’s exact tests. Survival to 90 days was compared between the hypotensive and normotensive response groups using (i) Kaplan–Meier analysis; (ii) Cox proportional hazards regression; and (iii) restricted mean survival time (RMST). The unadjusted RMST gives the mean survival time over a pre-specified time frame, reflecting the differences in areas under the Kaplan–Meier curves for each group. The RMST is not dependent on the proportional hazards assumption, and it reflects the entire time frame rather than instantaneous time points. In this case, the focus was on the early events, hence the time frame chosen was 90 days after LVAD implantation.

Covariates were chosen based on postulated associations and statistical significance on univariate exploratory analysis ($P < 0.2$). A $P$ value $<0.05$ was considered statistically significant for all tests. All statistical analyses were performed using Stata 16 (College Station, Texas).

## Results

Of the 432 individuals who underwent LVAD implantation between January 2011 and March 2022 at our institution, 210 were initially identified with an eligible CPX study. Fifty-four patients were subsequently excluded given their INTERMACS profile 1 or 2 at the time of LVAD implantation. Baseline characteristics of the final study cohort of 156 patients are detailed in Table 1. The median age was 63 years (IQR 54–69), the majority were male (90%) and 52% had underlying ischaemic cardiomyopathy. 58% and 47% had history of systemic hypertension and diabetes mellitus, respectively. HeartMate II (HM II, Abbott Laboratories, Minneapolis, MN, USA), HVAD (Medtronic Inc, Minneapolis, MN, USA) and HM III device utilization was 46%, 4%, and 51%, respectively. Eighty per cent of patients were classified as INTERMACS profiles 3–4 at the time of LVAD surgery. Hypotensive SBP response was recorded in 54 patients (35%) during the CPX study. The prevalence of ischaemic cardiomyopathy was slightly higher in LVAD recipients with hypotensive SBP response (63% vs. 46%), but there was no significant difference in any other demographic parameters, pre-LVAD laboratory values, implanted device type, and INTERMACS profile between the groups (Table 1).

CPX results for the cohort at large and subpopulations are detailed in Table 2. The duration of exercise was not statistically different between the groups with normal and hypotensive SBP response ($P = 0.054$). Mean VO$_{2\text{max}}$ was significantly lower in the hypotensive cohort (12.5 ± 4.2 vs. 10.4 ± 3.1; $P = 0.0014$) but the difference in V$\text{t}$/VCO$_2$ slope did not reach statistical significance (41.2 ± 12.5 vs. 45.3 ± 12.5; $P = 0.056$). While resting SBP values were similar, there was a 15 ± 12 mmHg increase in the cohort with normal SBP response versus a 13 ± 11 mmHg decrease in the hypotensive group (Table 2). The primary reason for CPX termination was similar in both cohorts except for a clinically significant drop in SBP, and included fatigue, dyspnoea, dizziness, chest discomfort, claudication, and joint pain (data not shown). The median number of days between completing the CPX and LVAD implantation was not statistically different at 43 (21–94) and 53 (20–133) days in the hypotensive and normal SBP response groups, respectively ($P = 0.68$).

Seven patients (13%) died during the index admission for LVAD implantation from the hypotensive cohort while only two (2%) from the group with normal SBP response ($P = 0.01$, Table 3). Mortality rates both at 30 days (7 vs. 1;
Table 2 CPX parameters of the study population and comparison between patients with normal and hypotensive blood pressure response to exercise

| Variable                        | Full cohort (n = 156) | Normal SBP response (n = 102) | Hypotensive SBP response (n = 54) | P-value |
|---------------------------------|-----------------------|-------------------------------|----------------------------------|---------|
| Exercise duration, min          | 6.6 ± 3.4             | 7.0 ± 3.4                     | 5.9 ± 3.4                        | 0.054   |
| Peak METs achieved              | 3.5 ± 1.3             | 3.8 ± 1.3                     | 3.1 ± 1.2                        | 0.0015  |
| VO2max, mL/kg/min               | 11.8 ± 4.0            | 12.5 ± 4.2                    | 10.4 ± 3.1                       | 0.0014  |
| V\textsubscript{E}/V\textsubscript{CO2} slope | 42.6 ± 12.6       | 41.2 ± 12.5                   | 45.3 ± 12.5                      | 0.056   |
| Respiratory exchange ratio, RER | 1.07 ± 0.13           | 1.08 ± 0.13                   | 1.06 ± 0.12                      | 0.50    |
| Resting systolic BP, mmHg       | 99 ± 14               | 98 ± 14                       | 101 ± 12                         | 0.10    |
| Resting diastolic BP, mmHg      | 65 ± 10               | 64 ± 10                       | 66 ± 10                          | 0.094   |
| Peak systolic BP, mmHg          | 104 ± 21              | 112 ± 20                      | 88 ± 13                          | N/A     |
| Peak diastolic BP, mmHg         | 61 ± 13               | 64 ± 13                       | 55 ± 9                           | <0.0001 |
| Exercise-induced change in systolic BP, mmHg | 5.1 ± 18             | 15 ± 12                       | −13 ± 11                         | N/A     |

BP, blood pressure; SBP, systolic blood pressure; MET, metabolic equivalent; VO2max, oxygen consumption at peak exercise; V\textsubscript{E}/V\textsubscript{CO2}, ventilatory equivalent of carbon dioxide. All data presented as mean ± standard deviation.

Table 3 Clinical variables collected and evaluated during the index hospital stay for LVAD implantation

| Variable                          | Full cohort (n = 156) | Normal SBP response (n = 102) | Hypotensive SBP response (n = 54) | P-value |
|-----------------------------------|-----------------------|-------------------------------|----------------------------------|---------|
| Mortality on index admission, n   | 9 (6%)                | 2 (2%)                        | 7 (13%)                          | 0.01    |
| 30 day mortality, n               | 8 (5%)                | 1 (1%)                        | 7 (13%)                          | 0.003   |
| 90 day mortality, n               | 11 (7%)               | 2 (2%)                        | 9 (17%)                          | 0.001   |
| Intensive care length of stay, days (median, IQR) | 6 (4–9)               | 6 (4–8)                       | 6 (4–9)                          | 0.91    |
| Length of index hospital stay, days (median, IQR) | 15 (12–24)            | 16 (13–27)                    | 15 (10–23)                       | 0.19    |
| Vasoactive medication use, days (median, IQR) | 3 (2–8)               | 3 (2–7)                       | 5 (2–8)                          | 0.83    |
| Length of mechanical ventilation, days (median, IQR) | 2 (2–4)               | 2 (2–4)                       | 3 (2–4)                          | 0.89    |
| Length of inhaled pulmonary vasodilator use, days (median, IQR) | 0 (0–3)               | 0 (0–2)                       | 0 (0–3)                          | 0.85    |
| Severe RV failure requiring RVAD support, n | 6 (4%)               | 3 (3%)                        | 3 (6%)                           | 0.42    |
| Liver failure, n                  | 9 (6%)                | 5 (5%)                        | 4 (7%)                           | 0.38    |
| Need for temporary haemodialysis after LVAD implantation, n | 10 (6%)               | 5 (5%)                        | 5 (9%)                           | 0.23    |
| Freedom from readmission at 90 days | 94 (65%)              | 65 (65%)                      | 29 (64%)                         | 0.95    |

SBP, systolic blood pressure; IQR, interquartile range; RV, right ventricle; RVAD, right ventricular assist device.

P = 0.003) and 90 days (9 vs. 2; P = 0.001) were significantly higher in the hypotensive cohort. Kaplan–Meier survival curves to 90 days are shown in Figure 1. The leading causes of death were persistent vasopelgia unresponsive to multiple vasoactive agents including angiotensin II and cerebrovascular events not directly related to the surgery. Using Cox regression models to adjust for age, INTERMACS profile (Model 1) or age, INTERMACS profile, serum creatinine, and total bilirubin (Model 2) did not affect the result quantitatively (Table 4). The RMST analysis showed that survival time was 10 days longer on average for the normal SBP response group compared with the hypotensive group over the 90 days post-LVAD implantation period (Table 4). This result remained after adjustment for the same covariates as those used for the Cox regression analysis (age and INTERMACS profile [Model 1]; age, INTERMACS profile, serum creatinine and total bilirubin [Model 2]). A single patient from the hypotensive group underwent heart transplantation 70 days after the LVAD surgery.

There were no significant differences between the groups in any of the variables pertinent to the index hospital admission for LVAD implantation (Table 3). Three patients from each cohort required temporary mechanical right ventricular support and the overall incidence of liver failure and acute renal failure requiring haemodialysis were low. Freedom from all-cause readmission at 90 days among the 147 patients who discharged from the hospital following LVAD surgery was 65% and 64% in the groups with normal and hypotensive SBP response, respectively (P = 0.95).

HeartMate III subgroup analysis

Seventy-nine patients underwent HM III device implantation in our cohort and 26 (33%) developed hypotensive SBP response during routine pre-LVAD CPX (Supporting Information, Table S1). Ischaemic cardiomyopathy was more prevalent (69% vs. 38%; P = 0.008) and serum creatinine was...
higher (1.44 mg/dL vs. 1.15 mg/dL; \( P = 0.013 \)) in the hypotensive group. Only 4% of patients were INTERMACS profile 5–6 at the time of implant surgery.

CPX results for the HM III cohort are shown in Supporting Information, Table S2. There was no significant difference in exercise duration and the \( V_{E}/V_{CO_2} \) slope between those with normal and hypotensive SBP response. Mean \( VO_2_{max} \) was significantly lower (10.0 ± 3.7 vs. 12.7 ± 4.7; \( P = 0.014 \)) in the hypotensive group. While resting SBP readings were similar, it increased by a mean of 14 ± 11 mmHg and decreased by 15 ± 13 mmHg in those with normal and hypotensive SBP response, respectively. The median number of days between CPX completion and LVAD implantation was similar (data not shown; \( P = 0.79 \)).

Mortality rates during index admission (7 vs. 1; \( P = 0.001 \)), at 30 days (6 vs. 1; \( P = 0.004 \)), and 90 days (7 vs. 2; \( P = 0.005 \)) were significantly higher in the group with hypotensive SBP response (Supporting Information, Table S3). Kaplan–Meier survival curves for HM III recipients are presented in Figure 2. Mirroring the cohort at large, the curves separate early with significantly lower survival rates in the hypotensive group both at 30 and 90 days. The unadjusted hazard ratio was 8.10 (1.68–39, 95% CI; \( P = 0.0091 \)). Cox regression models adjusted for age and INTERMACS profile (Model 1) or age, INTERMACS profile, serum creatinine and total bilirubin (Model 2) yielded similar results. RMST analysis revealed an average 17 days longer survival over the 90 days post-LVAD implantation period for patients with normal versus hypotensive SBP response when using Model 1. The survival advantage using Model 2 was 13 days.

Post-LVAD temporary dialysis was more frequent in patients with hypotensive SBP response (15% vs. 2%; \( P = 0.038 \)), but there were no significant differences in any of the other variables between the groups pertinent to the index hospital admission. Freedom from readmission at 90 days was also similar (69% vs. 83%; \( P = 0.20 \)).

Discussion

To our knowledge, this is the first study to investigate the association between hypotensive SBP response on CPX and 90 day mortality following durable LVAD implantation in a contemporary cohort. The overall prognostic value of BP measured in the ambulatory setting is well-established in

![Figure 1](image)

**Figure 1** Kaplan–Meier survival curves for the groups with hypotensive and normal systolic blood pressure response; 90 day survival was significantly lower for patients with hypotensive SBP response on routine pre-LVAD CPX study.

| Model | Cox model | RMST analysis |
|-------|-----------|---------------|
|       | HR (95% CI) | \( P \)-value | Normal SBP response (days) | Hypotensive SBP response (days) | Differential (days) | \( P \)-value |
| Unadjusted | 9.16 (1.98–42) | 0.0046 | 89 (87–91) | 79 (72–86) | 9.9 (2.6–17) | 0.008 |
| Model 1 | 9.05 (1.94–42) | 0.050 | 9.9 (2.5–17) | 0.009 |
| Model 2 | 9.98 (2.00–50) | 0.0051 | 9.2 (1.9–16) | 0.014 |

SBP, systolic blood pressure.

Model 1 is adjusted for age and INTERMACS profile. Model 2 is adjusted for age, INTERMACS profile, serum creatinine and total bilirubin.

| SBP, systolic blood pressure. |
|-----------------------------|

ESC Heart Failure 2022; 9:3496–3504
DOI: 10.1002/ehf2.14099
the general population as well as in patients with systolic heart failure.16–22 With the widespread availability of exercise stress testing, multiple cohort studies have shown that attenuated or hypotensive SBP response during exercise are powerful and independent predictors of all-cause and cardiovascular mortality as well as non-fatal adverse events.10,23–29 Similar findings were reported in individuals with chronic HF who underwent CPX.11,12,30–32

Accurately predicting survival and clinical outcomes following LVAD implantation is of critical importance and may affect the intensity of pre-surgical hemodynamic optimization and timing of the operation. In addition, an unfavourable risk–benefit ratio can potentially influence the decision making by the medical team to recommend heart transplantation in eligible individuals. Several risk stratification tools have been developed aiming to identify patients at increased peri-operative and post-operative mortality, including the Seattle Heart Failure Model,33 Destination Therapy Risk Score,34 HeartMate II Risk Score,35 Model for End-stage Liver Disease,36 and the Penn-Columbia risk score.37 Despite the widespread use of CPX to risk stratify patients with advanced HF, the only tool to incorporate gait speed and VO$_{2\max}$ is the Cardiac Outcomes Risk Assessment (CORA) model.38 The potential prognostic value of hypotensive versus normal SBP response on routine pre-LVAD CPX has not been systematically evaluated. Our study aims to address this critical gap.

In our final cohort of 156 patients, the prevalence of hypotensive SBP response on CPX performed within a median of 49 days prior to LVAD implantation was 35%. All-cause mortality on index admission, at 30 days and at 90 days was significantly higher in this group versus those with normal SBP response. Mortality rates became more similar between the groups beyond 90 days suggesting that hypotensive SBP response on pre-LVAD CPX has an added value in predicting clinical outcomes during the index surgical admission and the first three postoperative months. Cox regression analysis confirmed that this finding was independent of age, INTERMACS profile, serum creatinine and total bilirubin. The most common cause of death was significant and prolonged vasoplegia with the exact underlying mechanism yet to be identified. All-cause readmission rates at 90 days were comparable between the cohorts. Overall, our readmission rates are similar to that published in the most recent INTERMACS analysis.39

A sub-analysis of the HM III cohort was also performed given its increased utilization over the past years and that it is currently the only available LVAD for de-novo implantation in the USA. Similar to the cohort at large, hypotensive SBP response on pre-implantation CPX was a strong predictor of adverse clinical outcomes during the index admission, at 30 days as well as 90 days. In fact, 7 of 26 patients (27%) from the HM III cohort versus 2 of 26 (8%) patients from the HM II group with a hypotensive SBP on CPX died within 90 days of implantation. The underlying reason for the difference in mortality remains unclear but may be related to the difference in pump hemodynamic profiles, intrinsic flow patterns, or implantation technique. Nevertheless, our finding emphasizes the relevance of hypotensive SBP on pre-LVAD CPX in the current era and the importance to include this readily available binary variable in our clinical decision making regarding advanced heart failure therapies.

We have to acknowledge that the median VO$_{2\max}$ value was significantly lower and V/$\dot{E}$/VO$_{2\max}$ slope was higher, although not statistically significant, in the cohort with hypotensive SBP response. This finding is not surprising and suggests that, despite a lack of difference in INTERMACS profiles, patients in the hypotensive group may have slightly more advanced disease on the HF spectrum. It is important to emphasize that values for VO$_{2\max}$ and V/$\dot{E}$/VO$_{2\max}$ slope are on a continuum and, while these predict clinical outcomes
in general, they do not allow for granular individual risk stratification. We do not imply to alter surgical plans solely based on SBP response, but supplementing routine CPX data with a binary variable that is immediately available (normal vs. hypotensive SBP response) may allow for more individualized risk prediction prior to LVAD implantation. If our findings are successfully replicated in larger cohorts, hypotensive BP response on CPX may be incorporated into contemporary risk prediction tools. Ultimately, this information may help guide physician-patient discussions, determine optimal surgical timing, and promote optimized post-operative management.

Limitations

There are multiple limitations to the present study. First, this is a retrospective, single centre analysis with a relatively low number of patients in the final cohort. One hundred fifty-six of the 432 consecutive patients reviewed met our inclusion criteria. This is primarily due to the fact that pre-LVAD CPX was less commonly performed before 2015, but its utilization increased steadily over time as our clinical practice evolved. Second, patients in general with INTERMACS profiles 1 and 2 at the time of LVAD implantation are unable to complete a functional assessment or experienced rapid worsening in their clinical condition after the CPX. Therefore, these patients were excluded from the current analysis. Third, the majority of our population were males, and it remains unclear if our observations hold true for women. Large scale, prospective, multi-centre studies will be necessary to extend and validate our findings.

Conclusions

To our knowledge, this is the first study to demonstrate in a contemporary cohort that hypotensive SBP response during pre-LVAD CPX identifies a patient population with increased mortality on index admission as well as at 30 and 90 days. This finding suggests that SBP response, when used as a binary variable in addition to VO2max and VE/VCO2 slope, may enhance individual risk prediction for LVAD candidates. Additional studies are needed to validate these findings and determine the underlying mechanisms of the increased mortality observed in this cohort.

Funding

No funding was received for this study.

Conflict of interest

V. Maharaj: None. A. Agdamag: None. S. Duval: None. J. Edmiston: None. V. Charpentier: None. M. Fraser: None. J. Schultz: None. A. Hall: None. R. John: Consultant; Current/On-going - Payment Made to Me; Abbott Lab, Medtronic. Grant/Research Support; Current/On-going - Payment Made to Me; Abbott Lab, Medtronic. A. Shafer: None. C. Martin: None. T. Thenappan: None. G. Francis: NIH (research grant), NOVARTIS/MyoKardia DSMBs. R. Cogswell: Consultant; Current/On-going - Payment Made to Me; Abbott Lab, Medtronic. Speaker’s Bureau; Current/On-going - Payment Made to Me; Abbott Lab, Medtronic. Other Advisory Board Member; Current/On-going - Payment Made to Me; Medtronic. Other Financial or Material Support; Current/On-going - Payment Made to Me; Medtronic. T. Alexy: Speaker’s Bureau; Current/On-going - Payment Made to Me; Abbott Lab. Other Financial or Material Support; Current/On-going - Payment Made to Me; Boston Scientific.

Supporting information

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

Table S1. Baseline characteristics of the HeartMate III cohort. Comparison is shown between the groups with normal and hypotensive blood pressure response during routine pre-LVAD CPX. SBP: Systolic blood pressure; SD: Standard deviation; ICM: Ischemic cardiomyopathy; NICM: Non-ischemic cardiomyopathy; BMI: Body mass index.

Table S2. CPX parameters of the HeartMate III cohort and comparison between patients with normal and hypotensive blood pressure response to exercise. BP: Blood pressure; SBP: Systolic blood pressure; MET: Metabolic equivalent; VO2max: Oxygen consumption at peak exercise; VE/VCO2: Ventilatory equivalent of carbon dioxide. All data presented as mean±standard deviation.

Table S3. Clinical variables collected and evaluated during the index hospital stay for LVAD implantation in the HeartMate III cohort. SBP: Systolic blood pressure; IQR: Interquartile range; RV: Right ventricle; RVAD: Right ventricular assist device.

Table S4. Association of systolic blood pressure response and survival at 90 days after HeartMate III LVAD implantation from a) Cox regression analysis and b) RMST analysis. Model 1 is adjusted for age and INTERMACS profile. Model 2 is adjusted for age, INTERMACS profile, serum creatinine and total bilirubin. SBP: Systolic blood pressure.
References

1. Wasserman K, Whipp BJ, Koyl SN, Beaver WL. Anaerobic threshold and respiratory gas exchange during exercise. J Appl Physiol. 1973; 35: 236–243.

2. Weber KT, Kinasewitz GT, Janicki JS, Fishman AP. Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. Circulation. 1982; 65: 1213–1223.

3. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation. 1991; 83: 778–786.

4. Arena R, Myers J, Aslam SS, Varughese EB, Peberdy MA. Peak VO2 and VE/VCO2 slope in patients with heart failure: A prognostic comparison. Am Heart J. 2004; 147: 354–360.

5. Butler J, Khadim G, Paul KM, Davis SF, Kronenberg MW, Chomsky DB, Pierson RN. Selecting patients for heart transplantation in the current era of heart failure therapy. J Am Coll Cardiol. 2004; 43: 787–793.

6. Myers J, Gullestad L, Vagelos R, Do D, Bellin D, Ross H, Fowler MB. Clinical, hemodynamic, and cardiopulmonary exercise test determinants of survival in patients referred for evaluation of heart failure. Ann Intern Med. 1998; 129: 286–293.

7. Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, Long JW, Aschheim DF, Tierney AR, Levitan RG, Watson JT, Ronan NS, Shapiro PA, Lazar RM, Miller LW, Gupta L, Frazier OH, Desvigne-Nickens P, Oz MC, Poirier VL, Meier P. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med. 2001; 345: 226–233.

8. Mehra MR, Uriel N, Naka Y, Cleveland JC Jr, Yuzefpolskaya M, Salerno CT, Walsh MN, Milano CA, Patel CB, Hutchins SW, Rangos J, Ewald GA, Itoh K, Paganini OH, Desvigne-Nickens P, Oz MC, Poirier VL, Meier P. Long-term use of a left ventricular assist device for end-stage heart failure. N Engl J Med. 2001; 345: 226–233.

9. Lauer MS, Levy D, Anderson KM, Plehn D, Edmunds LH Jr, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation. 1991; 83: 778–786.

10. O’Neal WT, Qureshi WT, Blaha MJ, Ketyeyian SJ, Brawner CA, Al-Mallah MH. Systolic blood pressure response during exercise stress testing: The Henry ford Exercise testing (FIT) project. J Am Heart Assoc. 2015; 4: e002050.

11. Nishiyama Y, Morita H, Harada H, Katoh A, Adachi H, Koga Y, Ibeda H. Systolic blood pressure response to exercise as a predictor of mortality in patients with chronic heart failure. Int Heart J. 2010; 51: 111–115.

12. Kallistratos MS, Poulimenos LE, Pavlidis AN, Dritsas A, Laoutaris ID, Manolis AJ, Kokkinis DV. Prognostic significance of blood pressure response to exercise in patients with systolic heart failure. Heart Vessels. 2012; 27: 46–52.

13. Il’giovine ZJ, Solomon N, Devore AD, Wojdyla D, Patel CB, Rogers JG. Blood pressure response during cardiopulmonary exercise testing in heart failure. Med Sci Sports Exerc. 2018; 50: 1345–1349.

14. Bansal SAA. Clinical significance of blood pressure levels during treadmill exercise. Test Hypert J. 2015; 1: 83–87.

15. Lauer MS, Skin PM, Pashkow FJ, Snader CE, Marwick TH. Impaired chronotropic response to exercise stress testing as a predictor of mortality. JAMA. 1999; 281: 524–529.

16. Franklin SS, Wong ND. Hypertension and cardiovascular disease: Contributions of the Framingham heart study. Glob Heart. 2013; 8: 49–57.

17. Rutan GH, Kuller LH, Neaton JD, Wentworth DN, McDonald RH, Smith WM. Mortality associated with diastolic hypertension and isolated systolic hypertension among men screened for the multiple risk factor intervention trial. Circulation. 1988; 77: 504–514.

18. Leverington S, Clarke R, Qizilbash N, Peto R, Collins R, Prospective SC. Age-specific relevance of usual blood pressure to vascular mortality: A meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002; 360: 1903–1917.

19. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Danesh S, White IR, Cauley MF, Deanfield JE, Smeeth L, Williams B, Hingorani A, Hemingway H. Blood pressure and incidence of cardiovascular diseases: Lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. Lancet. 2014; 383: 1899–1911.

20. Guider G, Franz S, Bruersachs J, Alloio B, Wanner C, Koller MT, Ertl G, Angermann CE, Ströth S. Reverse epidermiology in systolic and nonsystolic heart failure: Cumulative prognostic benefit of classical cardiovascular risk factors. Circ Heart Fail. 2009; 2: 563–571.

21. Lee TT, Chen J, Cohen DJ, Tsao L. The association between blood pressure and mortality in patients with heart failure. Am Heart J. 2006; 151: 76–83.

22. Raphael CE, Whinnett ZL, Davies JE, Fontana M, Ferenczi EA, Manisty CH, Mayet J, Francis DP. Quantifying the paradoxical effect of higher systolic blood pressure on mortality in chronic heart failure. Heart. 2009; 95: 56–62.

23. Oliotto I, Maron BJ, Montenegro A, Mazzuoli F, Dolar A, Cecchi F. Prognostic value of systemic blood pressure response during exercise in a community-based patient population with hypertrophic cardiomyopathy. J Am Coll Cardiol. 1999; 33: 2044–2051.

24. Sharman JE, LaGerche A. Exercise blood pressure: Clinical relevance and correct measurement. J Hum Hypertens. 2015; 29: 351–358.

25. Barlow PA, Otahal P, Shultz MG, Shing CM, Sharman JE. Low exercise blood pressure and risk of cardiovascular events and all-cause mortality: Systematic review and meta-analysis. Atherosclerosis. 2014; 237: 13–22.

26. Gupta MP, Polena S, Coplan N, Panagopoulos G, Dhingra C, Myers J, Felicier M. Prognostic significance of systolic blood pressure response during exercise stress testing in men during exercise stress testing. Am J Cardiol. 2007; 100: 1609–1613.

27. de Liefde II, Hoeks SE, van Gestel YR, Klein J, Verhagen HJ, van Domburg RT, Poldermans D. Prognostic value of hypotensive blood pressure response during single-stage exercise test on long-term outcome in patients with known or suspected peripheral arterial disease. Coron Artery Dis. 2008; 19: 603–607.

28. Spilia K, Tikkakoski A, Alanko S, Saarala A, Hernesniemi J, Lyytikainen LP, Viik J, Lehtimäki T, Nieminen T, Nikus K, Kähönen M. Combination of low blood pressure response, low exercise capacity and slow heart rate recovery during an exercise test significantly increases mortality risk. Ann Med. 2014; 46: 390–396.

29. Dunkelgrun M, Hoeks SE, Elhendy A, van Domburg RT, Bax JJ, Noordzij PG, Feringa HH, Vidakovic R, Karagiannis SE, Schouten O, Poldermans D. Significance of hypotensive blood pressure response during dobutamine stress echocardiography. Int J Cardiol. 2008; 125: 358–363.

30. Osaka N, Chaitman BR, Miller LW, Yip D, Cishek MB, Wolford TL, Donohue TJ. Cardiopulmonary exercise testing identifies low risk patients with heart failure and severely impaired exercise capacity considered for heart transplantation. J Am Coll Cardiol. 1998; 31: 577–582.

31. Fagard R, Pardaens K, Vanhaecke J. Prognostic significance of exercise versus resting blood pressure in patients with chronic heart failure. J Hypertens. 1999; 17: 1977–1981.

32. Williams SG, Jackson M, Ng LL, Barker D, Patwala A, Tan LB. Exercise duration and peak systolic blood pressure are predictive of mortality in ambulatory pa-
tients with mild-moderate chronic heart failure. *Cardiology.* 2005; **104**: 221–226.

33. Ketchum ES, Moorman AJ, Fishbein DP, Mokadam NA, Verrier ED, Aldea GS, Andrus S, Kenyon KW, Levy WC. Predictive value of the Seattle heart failure model in patients undergoing left ventricular assist device placement. *J Heart Lung Transplant.* 2010; **29**: 1021–1025.

34. Teuteberg JJ, Ewald GA, Adamson RM, Lietz K, Miller LW, Tatooles AJ, Kormos RL, Sundareswaran KS, Farrar DJ, Rogers JG. Risk assessment for continuous flow left ventricular assist devices: Does the destination therapy risk score work? An analysis of over 1,000 patients. *J Am Coll Cardiol.* 2012; **60**: 44–51.

35. Cowger J, Sundareswaran K, Rogers JG, Park SJ, Pagani FD, Bhat G, Jaski B, Farrar DJ, Slaughter MS. Predicting survival in patients receiving continuous flow left ventricular assist devices: The HeartMate II risk score. *J Am Coll Cardiol.* 2013; **61**: 313–321.

36. Matthews JC, Pagani FD, Haft JW, Koelling TM, Naftel DC, Aaronson KD. Model for end-stage liver disease score predicts left ventricular assist device operative transfusion requirements, morbidity, and mortality. *Circulation.* 2010; **121**: 214–220.

37. Birati EY, Hanff TC, Maldonado D, Grandin EW, Kennel PJ, Mazurek JA, Vorovich E, Seigerman M, Howard JLL, Acker MA, Naka Y, Wald J, Goldberg LR, Jessup M, Atluri P, Margulies KB, Schulze PC, Rame JE. Predicting Long term outcome in patients treated with continuous flow left ventricular assist device: The Penn-Columbia risk score. *J Am Heart Assoc.* 2018; 7: e006408.

38. Kanwar MK, Lohmueller LC, Kormos RL, Teuteberg JJ, Rogers JG, Lindenfeld J, Bailey SH, McIlvennan CK, Benza R, Murali S, Antaki J. A Bayesian model to predict survival after left ventricular assist device implantation. *JACC Heart Fail.* 2018; 6: 771–779.

39. Kormos RL, Cowger J, Pagani FD, Teuteberg JJ, Goldstein DJ, Jacobs JP, Higgins RS, Stevenson LW, Stehlik J, Atluri P, Grady KL, Kirklin JK. The Society of Thoracic Surgeons Intermacs database annual report: Evolving indications, outcomes, and scientific partnerships. *Ann Thorac Surg.* 2019; **107**: 341–353.