Echocardiographic Evaluation of Left Ventricular Recovery After Refractory Out-of-Hospital Cardiac Arrest

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Abstract

Background:

The mechanisms and degree of myocardial recovery during treatment with venoarterial extracorporeal membrane oxygenation (VA-ECMO) are unclear. We performed a descriptive study to evaluate myocardial recovery and changes in parameters of myocardial loading using echocardiography.

Methods:

We used a retrospective cohort design to evaluate patients with refractory ventricular tachycardia/ventricular fibrillation out-of-hospital cardiac arrest who were treated with the Minnesota Resuscitation Consortium protocol. Left ventricular ejection fraction (LVEF), end-diastolic diameter (LVEDD), end-systolic diameter (LVESD), and fractional shortening were assessed using serial echocardiography. One-way analysis of variance (ANOVA) was used to compare parameters over six hospitalization stages. Two-way ANOVA was used to compare these parameters between patients that died during the index hospitalization and patients that survived.

Results:

77 patients had $\geq$1 echocardiographic turndown evaluations. Thirty-eight patients survived to discharge and 39 patients died. Of 39 in-hospital deaths, 17 patients died before VA-ECMO decannulation and 22 patients died after VA-ECMO decannulation. Among all patients, LVEF improved from 9.7±10.1% from the first echocardiogram after rewarming to 43.1±13.1% after decannulation ($p<0.001$) and fractional shortening ratio improved from 0.14±0.12 to 0.31±0.14 ($p<0.001$). The LVEDD and LVESD remained

stable ($p=0.36$ and $p=0.12$, respectively). Patients that died had a lower LVEF by an average of 6.93% (95% confidence interval: -10.0 to -3.83, $p<0.001$), but other parameters were similar.

Conclusion:

Refractory cardiac arrest patients treated with VA-ECMO experience significant recovery of ventricular function during treatment. We postulate that this primarily occurs via reduction of LV preload.

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Abbreviations and Acronyms

ANOVA: Analysis of Variance

CPR: Cardiopulmonary resuscitation

ECMO: Extracorporeal membrane oxygenation

IABP: Intra-aortic balloon pump

LV: Left ventricle

LVEDD: Left ventricular end-diastolic diameter

LVEF: Left ventricular ejection fraction

LVESD: Left ventricular end-systolic diameter

RV: Right ventricular

SBP: Systolic blood pressure

OHCA: Out-of-hospital cardiac arrest

VA-ECMO: Venoarterial extracorporeal membrane oxygenation

VF/VT: Ventricular fibrillation/ventricular tachycardia

Introduction

Cardiac arrest carries a significant mortality burden worldwide[1,2]. Percutaneous venoarterial extracorporeal membrane oxygenation (VA-ECMO) is emerging as an important supportive strategy for patients with cardiac arrest[2-4]. Percutaneous VA-ECMO provides hemodynamic support to allow for evaluation and treatment of reversible causes[2,5-8].

Animal and human data have suggested that VA-ECMO may increase left ventricular (LV) wall stress within hours of treatment and cause ventricular injury[9,10]. Thus, there has been considerable interest in the routine adjunctive extrication of LV blood to reduce myocardial wall stress, a process termed "unloading" the LV. Left ventricular unloading has been attempted with LV pigtail catheters[10,11], intra-aortic balloon pump (IABP) counter-pulsation[11], and percutaneous LV assist devices[12]. However, no consensus exists as to whether unloading strategies should be routinely employed to reduce LV wall stress. Additionally, few human data describe the natural evolution of cardiac recovery after significant acute cardiac injuries in patients treated with VA-ECMO. Finally, it is unclear how loading parameters correlate with echocardiographic evidence of ventricular recovery after acute cardiac injuries.

We conducted a descriptive study to characterize the echocardiographic sequence of ventricular recovery in a population of patients with refractory ventricular fibrillation/ventricular tachycardia (VT/VF) out-of-hospital cardiac arrest (OHCA) who were treated with percutaneous VA-ECMO. We also aimed to determine how echocardiographic parameters of LV loading changed with different levels of VA-ECMO support and with intra-aortic balloon pumps (IABP).

Methods

Study Population

We performed a descriptive study to evaluate patients that were hospitalized at the University of Minnesota Medical Center between December 1, 2015, and September 1, 2019 and were treated with the Minnesota Resuscitation Consortium refractory VT/VF protocol. This protocol has been described previously[3,4,13]. Percutaneous VA-ECMO is used with routine coronary angiography and a protocolized critical care pathway for patients presenting with OHCA due to refractory VT/VF. Adjunctive intra-aortic balloon pumps are used with VA-ECMO at the discretion of the treating interventional cardiologist if there is a lack of pulsatility after return of spontaneous circulation.

Echocardiographic Turndown Studies

During treatment with VA-ECMO, a transthoracic echocardiography turndown protocol was performed to evaluate hemodynamic and echocardiographic parameters after sequential decreases in the VA-ECMO circuit flow. Turndown echocardiography was used to guide decannulation. All patients had the IABP support discontinued prior to each turndown study. The first echocardiogram study was done after successful completion of the rewarming protocol >24 hours after the patient's hospital admission. The turndown studies were then performed daily until the patient was deemed suitable for decannulation or care was terminated.

The VA-ECMO flow was decreased every 3 minutes by approximately a half liter per minute to ≤2 L/minute. Heart rate, mean arterial pressure, arterial oxygen saturation

(SaO_2), mixed venous oxygen saturation, and left ventricular ejection fraction (LVEF) were assessed at each stage until the subject reached the lowest VA-ECMO flow. Mixed venous oxygen and arterial oxygen saturations were assessed via the VA-ECMO pump, mean arterial pressure via an arterial line, and LVEF via echocardiography.

The sonographer was instructed to obtain as many of the following standard views as needed for an accurate assessment of LVEF: parasternal long axis, parasternal short axis (at the aortic valve, mid-ventricle, and apex), apical 4-chamber view, apical 2-chamber view, apical 3-chamber view, and subcostal view. Diagnostic image quality was defined by the visualization of 15 of 17 segments in each study [14]. Contrast echocardiography with perflutren microbubbles was used at the sonographer's discretion to improve endocardial border definition.

All studies were evaluated by expert faculty readers. LVEF was quantified by the modified Simpson's "biplane method of disks" in accordance with our echocardiographic laboratory protocol. Where the sonographer was unable to obtain the requisite views to quantify LVEF by the modified Simpson's method, the area-length method was used per American Society of Echocardiography guidelines [14]. Fractional shortening was quantified using linear measurements of left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD) per the American Society of Echocardiography guidelines.[14] All disagreements in LVEF quantification were resolved by mutual consensus between two or more expert faculty readers.

Subjects were deemed suitable for decannulation when 3 criteria were met: 1) LVEF was >25% at VA-ECMO flows of ≤2 liters/minute with low or moderate inotropic support, 2) mean arterial pressure was maintained >55 mmHg under the same conditions, and 3) arterial oxygen saturation was >92% with <10 mmHg of positive end-expiratory pressure and <50% fraction of inspired oxygen concentration on the subject's ventilator. The IABP was also stopped during the turndown study. A cardiologist, a bedside nurse, and a VA-ECMO technician were present during all turndown studies. All echocardiographic studies were performed by the institution's registered diagnostic cardiac sonographers.

This turndown protocol was implemented as part of our clinical practice and data collection was part of a quality improvement project in this population. The University of Minnesota Institutional Review Board analysis (IRB number 1603M85246) approved the chart review and data analysis. Informed consent was waived.

Echocardiographic Evaluation of Recovery of Cardiac Function and Ventricular Unloading

Left ventricular ejection fraction (LVEF), LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), and fractional shortening were assessed at five stages in the hospitalization: the first echocardiogram of the hospitalization; the first turndown echocardiogram at the baseline (highest) and lowest VA-ECMO flow; and the last turndown echocardiogram study before decannulation or declaration of death at the baseline (highest) and lowest VA-ECMO flows. Where patients only had one turndown echocardiogram prior to decannulation, it was only included in the 'last turndown echocardiogram category' to prevent duplication of data. In patients who were successfully decannulated, we evaluated LVEDD, LVESD, fractional shortening, and LVEF at a sixth timepoint, the earliest echocardiogram after decannulation.

To evaluate myocardial loading, LVEDD was used as a surrogate for preload[15,16], and LVESD and systolic blood pressure (SBP) were used as surrogates for afterload[17,18]. Fractional shortening was also employed as a surrogate for afterload and LV efficiency[19,20]. The LVEF was used to measure functional recovery. Though these values have not been formally validated in the VA-ECMO population, LVEF and ventricular diameter have previously been used as measures of ventricular loading in patients receiving VA-ECMO support[21]. All expert echocardiography readers were blinded to the patient's survival outcome.

Data Collection and Statistical Analysis

Individual chart reviews were performed by faculty cardiologists. The clinical characteristics of patients who survived the index hospital hospitalization were compared with characteristics of those who did not survive the index hospitalization.

Continuous variables were compared using the t-test and presented as means with standard deviations or with the Wilcoxon-Rank sum test and presented as medians and interquartile ranges. Categorical variables were compared using the chi-squared test or the Fisher's exact test and reported as counts and proportions.

One-way analysis of variance (ANOVA) was used to compare LVEF, LVEDD, LVESD, and fractional shortening in the overall cohort over the course of the hospitalization. Two-way ANOVA was used to compare these parameters over the course of the hospitalization between patients that survived and those that died at the six stages of echocardiographic evaluation. A vital status group (survived or died during index hospitalization)*hospitalization stage multiplicative interaction was also evaluated. Normality and homogeneity of variance were evaluated using quantile-quantile and residual plots, respectively. Tukey's HSD test was used for post-hoc comparisons. The level of statistical significance was set at 0.05 for two-tailed hypothesis testing. All analyses were carried out in R and R Studio version 1.1.463[22].

Sensitivity Analyses

A sensitivity analysis was conducted to determine whether heemodynamic responses differed between patients that had an intra-aortic balloon pump (IABP) compared to those that only had VA-ECMO placement without any IABP. Two-way ANOVA was used to compare LVEF, LVEDD, LVESD, and fractional shortening, as above. An unloading group*hospitalization stage multiplicative interaction was evaluated.

A second sensitivity analysis was done to compare right ventricular (RV) function in patients that survived the index hospitalization to those that did not. The RV function was categorized as indeterminate, normal, mildly reduced, moderately reduced, or severely reduced, based on a qualitative visual assessment of RV function only. This was our echocardiography laboratory's protocol for echocardiographic examinations in patients being treated with VA-ECMO.

Results

Baseline Characteristics

One hundred seventy-two patients underwent VA-ECMO placement for refractory VT/VF OHCA between December 2015 and September 2019 (**Figure 1**). Ninety-five patients had care withdrawn before their first echocardiogram due to evidence of devastating neurologic injury or goals of care decisions that were made in the first 24 hours. Seventy-seven patients had >1 interpretable turndown echocardiograms and were included in the analyses.

There were more males among the patients who died during the index hospitalization (89.7% versus 68.4%, p=0.04; **Table 1**). Patients that died tended to be older and had a higher prevalence of congestive heart failure and coronary artery disease, but these differences were not significant. A high proportion of patients (68.9%) had received bystander cardiopulmonary resuscitation (**Table 2**). The patients presented after having received 5.00 (3.00, 7.00) defibrillatory shocks with a serum pH of 7.08 (6.97, 7.20) and an initial serum lactate of 11.4 (9.40, 13.9) mmol/L. Patients had VA-ECMO cannulation 8.00 (6.00, 11.0) minutes after presentation to our cardiac catheterization laboratory. All patients had coronary angiography and, if indicated, percutaneous coronary intervention. Sixty of 77 patients (77.9%) survived to decannulation. Aside from the proportion surviving to decannulation, there were no differences between patients that survived and died in these characteristics (**Table 2**).

Natural History of Cardiac Recovery

During the hospitalization, heart rate and mean arterial pressure progressively increased in the overall cohort (p<0.001 and p=0.035, respectively; **Table 3**). Pulse pressure remained stable (p=0.55). There were no differences in heart rates, SBP, mean arterial pressure, or pulse pressure between those that survived and those that died (p=0.86, p=0.15, p=0.11, and p=0.44, respectively) at any stage of the hospitalization. Patients underwent VA-ECMO decannulation 4.18 (3.09, 5.00) days after admission.

In the overall cohort, VA-ECMO flow was stable at ~3.70 L/min before the first echocardiogram after rewarming and final turndown echocardiograms (**Table 3**). The LVEF increased from 9.7±10.1% during the first echocardiogram after rewarming to 43.1±13.1% after decannulation (p<0.001; **Table 4** and **Figure 2**). The LVEDD remained stable in the overall cohort (p=0.36; **Figure 3)**. The LVESD trended downwards during the hospitalization from 3.9±1.2 cm in the first echocardiogram after rewarming to 3.6±0.9 cm after decannulation (p=0.12; **Figure 4**). Fractional shortening improved from 0.14±0.12 during the first echocardiogram after rewarming to 0.31±0.14 after decannulation (p<0.001; **Table 4** and **Figure 5**).

When comparing the patients that died and those that survived, the patients that died required, on average, 0.34 L/min more VA-ECMO flow (95% confidence interval: 0.19-0.49, p<0.001; **Table 4**) during each stage. Patients that died had a lower LVEF by an average of 6.93% (95% confidence interval: -10.0 to -3.83, p <0.001; **Figure 2**) during each stage compared to the patients that survived. Both groups exhibited a similar degree of improvement in LVEF (p<0.001; **Table 5**). There were no significant differences in LVEDD (p=0.36) or LVESD (p=0.80) by vital status group or hospitalization stage (**Figures 3** and **4**). Fractional shortening improved during the hospitalization [(p<0.001;

Figure 5 and **Table 6**], but there was no difference in the degree of improvement. The vital status group*hospitalization stage interaction was not significant for the LVEF, LVEDD, LVESD, or fractional shortening two-way ANOVA analyses comparing patients that survived and died.

Sensitivity Analyses

We compared the hemodynamic responses between patients that had IABPs placed (48/77) to those that did not have IABPs placed (29/77). Among these 48 patients, three patients had the IABP removed before VA-ECMO decannulation, 36 patients had the IABP removed at a median of 1.25 (0.78, 2.17) days after VA-ECMO decannulation, and nine patients died without having VA-ECMO decannulation or IABP removal. There were no differences in hemodynamics at the time of the first echocardiogram after decannulation or the time to ending targeted temperature management, vasopressors, or VA-ECMO decannulation in relation to the first echocardiogram after decannulation (**Table 7**). The LVEF rose steadily after the first echocardiogram in both groups ($p<0.001$; **Table 8**) without any difference among groups ($p=0.37$). The results of the two-way ANOVA for the LVEDD and LVESD were not significant ($p=0.59$ and $p=0.63$, respectively). There was no difference in SBP at any stage of the hospitalization between patients that had an IABP and those that did not ($p=0.11$). Fractional shortening improved over the course of the hospitalization in both groups (**Table 9**). Patients that had an IABP trended towards a higher fractional shortening ratio by (0.028, 95% confidence interval: 0.0008-0.056; $p=0.056$). The unloading group*hospitalization stage interaction was not significant in any of the above analyses.

In the second sensitivity analysis, the proportion of patients with normal RV function increased from 1.4% (1 of 72 patients) after rewarming to 70.4% (33 of 47 patients) in the after decannulation ($p<0.001$). Right ventricular function did not differ between the patients that survived and died during the index hospitalization (**Table 10**).

Discussion

Our investigation outlines the changes in ventricular function and loading in patients with refractory VT/VF arrest that were treated with a protocolized critical care pathway involving percutaneous VA-ECMO. In the overall cohort, LVEF, fractional shortening, and RV function improved over the course of the hospitalization while LVEDD and LVESD stayed stable. The patients that survived the index hospitalization had greater improvement in LVEF and required lower levels of VA-ECMO flow during the turndown echocardiograms compared to the patients that died. There were no differences in LVEDD, LVESD, or fractional shortening between patients that survived in the index hospitalization and those that died. In our sensitivity analyses, the patients that had an IABP exhibited similar changes in LVEF, LVEDD, LVESD, SBP, and fractional shortening compared to patients without IABPs. Collectively, this suggests that cardiac recovery is generally promoted by VA-ECMO, occurs in a time-dependent manner, and occurs regardless of whether an IABP is present or not.

The balance between heart rate, afterload and preload dictates stroke work, which consequently determines myocardial oxygen consumption[17]. It follows, then, that increased LVEDD (preload) and/or increased LVESD (afterload) increase wall stress and myocardial oxygen consumption[23,24]. Although preload remains difficult to characterize in patients with VA-ECMO, it should be low by definition since most of the blood bypasses the LV and transpulmonary flow is limited on full VA-ECMO support[25]. Our data support this by demonstrating that LVEDD, LVESD, and SBP are relatively stable in the overall cohort of patients. Thus, we speculate that, even if there is an increase in afterload after the institution of VA-ECMO, the decrease in preload may be more clinically relevant and prevent a dramatic rise in myocardial oxygen consumption. Subsequently lowering VA-ECMO support may allow for increased preload, then increased LV contractility and efficiency per the Frank-Starling Law. We noted that patients that had unloading devices had no differences in the LVEDD or LVESD compared to patients that did not have an IABP. This implied similar preload and afterload regardless of the presence of an IABP. Additionally, there was also a higher proportion of survivors in the group that did not receive an IABP (16/29 or 55.2%) compared to the group that received an IABP (22/48 or 45.8%). Thus, there may be other features to explain the differences in the patients that survived the index hospitalization and those that died. This could include differences in age, baseline comorbidities, rates of bystander CPR, and the ability of some patients to better manage the balance between contractility, systemic vascular resistance, and pulmonary vascular resistance with declining VA-ECMO support[26].

Schiller *et al*[9] initially suggested that VA-ECMO increases afterload within hours of institution and quickly leads to increased LV end-systolic volume, wall stress, and LV distension in their porcine model. Human studies have also suggested that VA-ECMO also increases afterload, producing a deleterious environment for myocardial recovery[10]. These observations have been used to rationalize routine adjunctive mechanical unloading[12,27]. However, our study showed that LVEF and RV function continued to improve even as LVEDD and LVESD remained stable or changed marginally while VA-ECMO support was withdrawn. Thus, based on our data, it seems unlikely that patients treated with VA-ECMO must combat extremely high, clinically relevant afterload. We speculate that the marked reduction in preload may offset any appreciable change in afterload, thus facilitating significant myocardial recovery after the index myocardial injury.

Other groups have also described the importance of identifying LV distension during VA-ECMO treatment and the importance of unloading. Truby *et al* described LV distension as a composite of a radiologic definition and elevated pulmonary artery diastolic pressure[28]. In their cohort, they noted that patients without LV distension, with subclinical LV distension, and with clinical LV distension had similar survival to discharge, though patients requiring left ventricular decompression had lower likelihood of myocardial recovery. However, their data did not have any measurements of LV diameter or volume to guide clinical decision-making. Our echocardiographic data may have incremental value in this regard. Pappalardo *et al* described lower mortality in patients with cardiogenic shock who were treated with VA-ECMO and percutaneous LV assist device compared to patients who were treated with only VA-ECMO in both unmatched and propensity-matched samples[27]. This study may also be subject to selection bias, given that the patients that had VA-ECMO and percutaneous LV assist device placement had a significantly higher pH at baseline (7.36) than patients that only had VA-ECMO (7.16). The investigators also employed 'maximal' speeds of VA-ECMO to normalize metabolic malperfusion. Higher circuit flows may worsen LV distension[15]. Finally, our study supports the utility of serial echocardiographic examination to monitor LV recovery in patients with treated VA-ECMO[29]. Our data are also consistent with prior suggestions that LVEF may guide prognosis in patients treated with VA-ECMO[29,30].

Our findings may have clinical implications. Our study demonstrates that patients with refractory VT/VT cardiac arrest can have significant ventricular recovery despite no appreciable mechanical contractility upon admission (due to their presentation with refractory ventricular tachycardia/ventricular fibrillation) and minimal recovery in the first 24 hours[3,5]. We also highlight that the management of cardiac arrest patients is highly resource-intensive and necessitates significant institutional expertise. Although ~75% of the patients in this investigation exhibited ischemic causes for refractory VT/VF/OHCA, this notion is also pertinent to patients with non-ischemic refractory VT/VF OHCA. Here, medical management and specialized ablative procedures may be important to prevent repeat VT/VF cardiac arrest. This supports the notion that cardiac arrest care should be managed in expert centers to maximize outcomes[31]. Finally, VA-ECMO usage in patients with refractory VT/VF cardiac arrest has previously been deemed to be a cost-effective therapy well within the identified quality-adjusted life-years limit[32]. Nevertheless, it remains expensive. Targeting the use of adjunctive devices and procedures for LV unloading to selected cases, rather than routine use, may serve to reduce overall procedures, ventilation time, haemolysis, renal replacement therapy, and hospitalization cost[27]. Alternative strategies such as aggressive afterload reduction with medical therapies (such as a lower MAP goal and aggressive afterload reduction), low flow rates on VA-ECMO, higher positive end-expiratory pressures during ventilation, and restrictive fluid management may offer utility in deferring unloading strategies[33].

Our investigation has several limitations. We use imaging data instead of in vivo measurements of myocardial stress during treatment with VA-ECMO. We were limited in our ability to obtain Doppler echocardiographic data or use invasive haemodynamics to further quantify LV dysfunction and recovery. Regardless, none of these metrics have been formally validated in patients on VA-ECMO. Our cohort is small and is prone to type II error. To the best of our knowledge, however, the Minnesota Resuscitation Consortium has the largest American cohort reporting outcomes of VA-ECMO treatment for refractory VT/VF OHCA. The occurrence of OHCA is due to a heterogenous set of aetiologies. This may also lead to differences in overall cardiac outcome. However, we have previously demonstrated that the vast majority of refractory VT/VF OHCA is associated with significant underlying coronary artery disease[5]. There were differences in the number of echocardiographic examinations at each stage in our investigation. This is because >40 patients only had one turndown prior to decannulation. Finally, decannulation from VA-ECMO and care withdrawal involves a complex interplay of decisions. We cannot capture all of them in our study.

Conclusions

Refractory VT/VF OHCA patients who were treated with VA-ECMO had significant biventricular recovery. Cardiac recovery appeared to be a time-dependent phenomenon that may occur via reduction of transpulmonary flow and LV preload without a clinically significant increase in afterload.

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Table 1. Patient Characteristics.

Characteristic	Overall Cohort n = 77	In-Hospital Vital Status Alive n = 38	Death n = 39	p Value*
Basic demographics				
Age, years	60.0 (49.1, 67.1)	56.9 (48.9, 65.3)	61.3 (54.3, 69.0)	**0.049**†
Male	61 (79.2%)	26 (68.4%)	35 (89.7%)	**0.04**
Background medical history				
Congestive heart failure	15 (19.5%)	5 (13.2%)	10 (25.6%)	0.25†
Coronary artery disease	21 (27.3%)	9 (23.7%)	12 (30.8%)	0.61
Prior myocardial infarction	10 (13.0%)	4 (10.5%)	6 (15.4%)	0.74†
Prior CABG	9 (11.7%)	3 (7.9%)	6 (15.4%)	0.48†
Prior PCI	10 (13.0%)	4 (10.5%)	6 (15.4%)	0.74†
Diabetes mellitus	18 (23.4%)	6 (15.8%)	12 (30.8%)	0.18
Dyslipidemia	29 (37.7%)	13 (34.2%)	19 (48.7%)	0.25
Hypertension	40 (51.9%)	20 (52.6%)	20 (51.3%)	>0.99
Tobacco usage	20 (25.9%)	13 (34.2%)	7 (18.0%)	0.13
Baseline medication history				
Aspirin	14 (18.2%)	5 (13.2%)	9 (23.1%)	0.38†
Angiotensin converting enzyme inhibitor	19 (24.6%)	6 (15.8%)	13 (33.3%)	0.11
Beta-blocker	16 (20.8%)	5 (13.2%)	11 (28.2%)	0.16†
P2y12 inhibitor	2 (2.6%)	2 (5.3%)	0 (0.0%)	0.24†

Table 1. Patient Characteristics.					
		In-Hospital Vital Status			
Characteristic	**Overall Cohort n = 77**	**Alive n = 38**	**Death n = 39**	**p Value***
Statin	20 (26.0%)	8 (21.1%)	12 (30.8%)	0.44

Normally distributed continuous data are expressed as mean ± standard deviation and non-normally distributed data are expressed as median (interquartile range). Categorical data are expressed as n (%).

*Difference between patients surviving the index hospitalization and patients that died during the index hospitalization.

† = Obtained with non-parametric testing.

Legend: CABG indicates coronary artery bypass grafting; PCI, percutaneous coronary intervention; VA ECMO, venoarterial extracorporeal membrane oxygenation.

Table 2. Characteristics of the Cardiac Arrest.				
Characteristic	**Overall Cohort n = 77**	**Alive n = 38**	**Death n = 39**	**p Value***
Presenting Characteristics				
Bystander cardiopulmonary resuscitation	53 (68.9%)	29 (76.3%)	24 (61.5%)	0.27
Initial lactate, mmol/L	11.8 ± 3.7	11.9 ± 4.2	11.6 ± 3.2	0.78
Initial pH	7.10 ± 0.21	7.09 ± 0.22	7.11 ± 0.18	0.67
Initial arterial oxygen, mmHg	90.0 (59.3, 254.0)	90.0 (52.0, 227.0)	90.0 (62.0, 288.0)	0.37†
Initial arterial carbon dioxide, mmHg	49.0 (40.5, 65.0)	39.0 (35.0, 42.0)	36.0 (30.0, 44.8)	0.74†
Initial serum bicarbonate, mg/dL	17.0 (14.0, 20.0)	16.0 (13.0, 19.0)	17.0 (15.0, 20.0)	0.13†
Total number of shocks	5.00 (3.00, 7.00)	5.00 (3.00, 7.00)	5.00 (3.00, 8.00)	0.59†
Coronary Angiography				
Coronary angiography performed	77 (100.0%)	38 (100.0%)	39 (100.0%)	>0.99
Number of diseased vessels on coronary angiography	2.00 (0.00, 3.00)	1.50 (2.00, 3.00)	2.00 (0.00, 3.00)	0.58†
None	20 (26.0%)	9 (23.7%)	11 (28.2%)	0.19†
One vessel	13 (16.9%)	10 (26.3%)	3 (7.7%)	
Two vessels	15 (19.5%)	6 (15.8%)	9 (23.1%)	
Three vessels	29 (37.7%)	13 (34.2%)	16 (41.0%)	
Total number of stents placed at index coronary angiogram	1.00 (0.00, 3.00)	1.00 (1.00, 3.00)	2.00 (0.00, 3.00)	0.27†

Table 2. Characteristics of the Cardiac Arrest.				
Characteristic	**Overall Cohort n = 77**	**Alive n = 38**	**Death n = 39**	**p Value***
Treatment				
Time to initiation of venoarterial extracorporeal membrane oxygenation, minutes	8.00 (6.00, 11.0)	8.00 (6.00, 11.0)	7.00 (5.00, 10.5)	0.11†
Intra-aortic balloon pump placement at index procedure	48 (62.3%)	22 (57.9%)	26 (66.7%)	0.58
Inotropes during hospitalization	62 (80.5%)	32 (84.2%)	30 (76.9%)	0.60
Vasopressors during hospitalization	74 (96.1%)	37 (97.4%)	37 (94.9%)	>0.99
Progression to decannulation	60 (77.9%)	38 (100.0%)	22 (56.4%)	**<0.001**
Time to first echocardiogram after admission, days	1.35 (0.70, 1.46)	1.33 (0.65, 1.40)	1.35 (1.17, 1.46)	0.17†
Time to first turndown after admission, days	2.55 (2.46, 3.42)	2.55 (2.46, 2.59)	2.95 (2.45, 3.74)	0.52†
Time to last turndown after admission, days	3.38 (2.48, 4.47)	3.40 (2.46, 3.59)	3.38 (2.48, 5.44)	0.33†
Time to decannulation after admission, days	4.18 (3.09, 5.00)	4.18 (3.44, 4.79)	4.21 (2.68, 5.52)	0.97†
Time to post-decannulation echocardiogram after admission, days	5.60 (4.45, 8.15)	5.60 (4.36, 8.15)	5.91 (5.10, 8.82)	0.84†

Normally distributed continuous data are expressed as mean ± standard deviation and non-normally distributed data are expressed as median (interquartile range). Categorical data are expressed as n (%).

*Difference between patients surviving the index admission and patients that died during the index hospitalization.

† = Obtained with non-parametric testing.

All 77 patients in the cohort had ≥1 turndown echocardiogram. There were 36 patients in each group that had an echocardiogram after completion of the warming protocol. Sixteen patients who survived and 12 patients who died had a second turndown echocardiogram. Thirty-one patients who survived had an echocardiogram after VA-ECMO decannulation and 16 patients who died had an echocardiogram after VA-ECMO decannulation.

Table 3. Hemodynamics During Hospitalization Stages.			
Parameter	**Total Cohort**	**Alive n = 38**	**Death n = 39**
Hemodynamics Prior to First Echocardiogram			
Heart rate, bpm	69.0 ± 18.5	68.0 ± 17.5	70.0 ± 19.7
Mean arterial pressure, mmHg	76.5 ± 16.4	74.9 ± 17.0	78.2 ± 15.9
Systolic blood pressure, mmHg	104.5 ± 25.4	101.7 ± 23.7	108.9 ± 27.0
Pulse pressure, mmHg	41.5 ± 25.7	39.3 ± 22.4	43.7 ± 28.7
Hemodynamics Prior to First Turndown			
Heart rate, bpm	80.3 ± 20.1	87.1 ± 17.4	71.2 ± 20.5
Mean arterial pressure, mmHg	71.7 ± 13.9	76.0 ± 14.0	65.0 ± 11.7
Systolic blood pressure, mmHg	98.8 ± 26.4	102.4 ± 25.6	94.0 ± 28.8
Pulse pressure, mmHg	40.0 ± 26.0	41.4 ± 28.8	37.6 ± 24.2
Hemodynamics Prior to Final Turndown Before Decannulation			
Heart rate, bpm	85.1 ± 18.2	83.9 ± 15.3	85.2 ± 20.4
Mean arterial pressure, mmHg	77.2 ± 12.3	78.8 ± 12.5	75.6 ± 12.1
Systolic blood pressure, mmHg	105.3 ± 19.1	106.2 ± 19.7	104.5 ± 18.9
Pulse pressure, mmHg	43.7 ± 20.7	42.8 ± 19.2	44.5 ± 22.2
Hemodynamics During First Echocardiogram After Decannulation			
Heart rate, bpm	88.3 ± 22.7	86.3 ± 22.2	92.1 ± 23.9
Mean arterial pressure, mmHg	81.9 ± 12.9	84.0 ± 12.9	77.8 ± 12.0

Table 3. Hemodynamics During Hospitalization Stages.			
Parameter	**Total Cohort**	**Alive n = 38**	**Death n = 39**
Systolic blood pressure, mmHg	113.4 ± 20.8	115.0 ± 21.6	110.8 ±19.6
Pulse pressure, mmHg	47.6 ± 21.4	46.6 ± 22.5	49.4 ± 19.6
VA-ECMO Circuit Flow (L/min)			
First echocardiogram after rewarming	3.7 ± 0.7	3.6 ± 0.7	3.9 ± 0.6
First turndown echocardiogram			
Highest flow	4.1 ± 0.6	3.9 ± 0.6	4.2 ± 0.5
Lowest flow	1.8 ± 0.5	1.4 ± 0.5	2.3 ± 0.9
Final turndown			
Highest flow	3.5 ± 0.7	3.4 ± 0.7	3.6 ± 0.7
Lowest flow	1.4 ± 0.6	1.3 ± 0.4	1.6 ± 0.7

Data are expressed as mean ± standard deviation.

Legend: L/min = Liters per minute; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; LVEF = left ventricular ejection fraction.

Table 4. Relationship of Ventricular Loading Parameters to Vital Status.			
Parameter	**Total Cohort**	**Alive** **n = 38**	**Death** **n = 39**
LVEF, %			
First echocardiogram after rewarming	9.7 ± 10.1	9.9 ± 9.9	9.6 ± 10.6
First turndown echocardiogram			
Highest flow	15.0 ± 12.0	17.6 ± 12.1	11.7 ± 11.4
Lowest flow	19.6 ± 14.3	22.4 ± 14.5	15.8 ± 13.8
Final turndown			
Highest flow	27.1 ± 16.6	32.7 ± 16.1	21.8 ± 15.5
Lowest flow	31.4 ± 17.4	35.9 ± 16.9	27.2 ± 16.7
After decannulation	43.1 ± 13.1	43.2 ± 12.6	42.9 ± 14.3
Change During Hospitalization	31.2 ± 15.6	32.1 ± 14.6	29.5 ± 17.8
LVEDD, cm			
First echocardiogram after rewarming	4.6 ± 1.1	4.4 ± 1.0	4.7 ± 1.2
First turndown echocardiogram			
Highest flow	4.6 ± 1.0	4.7 ± 1.1	4.5 ± 1.0
Lowest flow	4.5 ± 1.0	4.6 ± 1.0	4.4 ± 0.9
Final turndown			
Highest flow	4.5 ± 0.9	4.4 ± 0.9	4.6 ± 1.0
Lowest flow	4.6 ± 0.8	4.5 ± 0.9	4.6 ± 0.8
After decannulation	4.9 ± 0.8	4.9 ± 0.9	4.9 ± 0.7
Change During Hospitalization	0.4 ± 0.8	0.4 ± 0.8	0.4 ± 0.7

Table 4. Relationship of Ventricular Loading Parameters to Vital Status.			
Parameter	**Total Cohort**	**Alive n = 38**	**Death n = 39**
LVESD, cm			
First echocardiogram after rewarming	3.9 ± 1.2	3.8 ± 1.1	4.1 ± 1.2
First turndown echocardiogram			
Highest flow	4.0 ± 1.2	4.1 ± 1.3	3.9 ± 1.0
Lowest flow	3.7 ± 1.1	3.8 ± 1.3	3.6 ± 1.0
Final turndown			
Highest flow	3.6 ± 1.0	3.5 ± 1.0	3.7 ± 1.0
Lowest flow	3.5 ± 1.0	3.4 ± 1.0	3.6 ± 1.0
After decannulation	3.6 ± 0.9	3.6 ± 1.0	3.5 ± 0.9
Change During Hospitalization	-0.3 ± 1.0	-0.3 ± 1.1	-0.3 ± 1.0
Fractional shortening, %			
First echocardiogram after rewarming	0.14 ± 0.12	0.15 ± 0.12	0.13 ± 0.12
First turndown echocardiogram			
Highest flow	0.14 ± 0.10	0.14 ± 0.12	0.14 ± 0.09
Lowest flow	0.18 ± 0.12	0.18 ± 0.13	0.18 ± 0.10
Final turndown			
Highest flow	0.21 ± 0.10	0.22 ± 0.09	0.20 ± 0.11
Lowest flow	0.24 ± 0.12	0.26 ± 0.12	0.21 ± 0.12
After decannulation	0.31 ± 0.14	0.29 ± 0.12	0.36 ± 0.17
Change During Hospitalization	0.15 ± 0.18	0.14 ± 0.16	0.19 ± 0.21

Data are expressed as mean ± standard deviation.

Legend: LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; LVEF = left ventricular ejection fraction.

Table 5. Post-Hoc Comparisons for LVEF by Vital Status Group.				
Post-Hoc Comparison for LVEF by Stage	**Difference (Percentage)**	**Lower Bound of 95% Confidence Interval**	**Upper Bound of 95% Confidence Interval**	**$P_{adjusted}$**
First Turndown, Highest Flow – First Echocardiogram	4.80	-4.27	13.9	0.653
First Turndown, Lowest Flow – First Echocardiogram	9.34	0.27	18.4	**0.039**
Final Turndown, Highest Flow – First Echocardiogram	17.5	10.8	24.2	**<0.001**
Final Turndown, Lowest Flow –First Echocardiogram	21.8	15.1	28.5	**<0.001**
After Decannulation – First Echocardiogram	32.2	24.6	39.86	**<0.001**
First Turndown, Lowest Flow –First Turndown, Highest Flow	4.54	-6.35	15.4	0.84
Final Turndown, Highest Flow –First Turndown, Highest Flow	12.7	3.66	21.7	**<0.001**
Final Turndown, Lowest Flow – First Turndown, Highest Flow	17.0	7.95	26.0	**<0.001**
After Decannulation – First Turndown, Highest Flow	27.4	17.7	37.1	**<0.001**

Table 5. Post-Hoc Comparisons for LVEF by Vital Status Group.				
Final Turndown, Highest Flow – First Turndown, Lowest Flow	8.13	-0.87	17.1	0.10
Final Turndown, Lowest Flow – First Turndown, Lowest Flow	12.4	3.42	21.4	**<0.001**
After Decannulation – First Turndown, Lowest Flow	22.9	13.16	32.6	**<0.001**
Final Turndown, Lowest Flow –Final Turndown, Highest Flow	4.29	-2.32	10.9	0.43
After Decannulation – Final Turndown, Highest Flow	14.7	7.19	22.3	**<0.001**
After Decannulation – Final Turndown, Lowest Flow	10.5	2.90	18.0	**<0.001**

Table 6. Post-Hoc Comparisons for Fractional Shortening by Vital Status Group.				
Post-Hoc Comparison for Fractional Shortening by Stage	Difference in Ratio	Lower Bound of 95% Confidence Interval	Upper Bound of 95% Confidence Interval	Padjusted
First Turndown, Highest Flow – First Echocardiogram	0.001	-0.077	0.079	>0.99
First Turndown, Lowest Flow – First Echocardiogram	0.037	-0.043	0.116	0.77
Final Turndown, Highest Flow – First Echocardiogram	0.071	0.014	0.128	**<0.001**
Final Turndown, Lowest Flow – First Echocardiogram	0.098	0.041	0.156	**<0.001**
After Decannulation – First Echocardiogram	0.173	0.109	0.237	**<0.001**
First Turndown, Lowest Flow – First Turndown, Highest Flow	0.036	-0.060	0.131	0.89
Final Turndown, Highest Flow – First Turndown, Highest Flow	0.070	-0.008	0.148	0.11
Final Turndown, Lowest Flow – First Turndown, Highest Flow	0.097	0.019	0.176	**0.0058**
After Decannulation –	0.172	0.088	0.255	**<0.001**

Table 6. Post-Hoc Comparisons for Fractional Shortening by Vital Status Group.				
First Turndown, Highest Flow				
Final Turndown, Highest Flow – First Turndown, Lowest Flow	0.034	-0.045	0.113	0.82
Final Turndown, Lowest Flow – First Turndown, Lowest Flow	0.061	-0.018	0.141	0.23
After Decannulation – First Turndown, Lowest Flow	0.136	0.052	0.221	**<0.001**
Final Turndown, Lowest Flow – Final Turndown, Highest Flow	0.027	-0.030	0.085	0.74
After Decannulation – Final Turndown, Highest Flow	0.102	0.038	0.166	**<0.001**
After Decannulation – Final Turndown, Lowest Flow	0.075	0.010	0.139	**0.013**

Table 7. Clinical Timepoints in Relation to First Echocardiogram After Decannulation.				
Clinical Timepoint (Days)	**All Patients with Echocardiograms After VA-ECMO Decannulation n = 47**	**Patients with Adjunctive Unloading Devices n = 29**	**Patients without Adjunctive Unloading Devices n = 18**	**P value***
Time from ending therapeutic temperature management to first echocardiogram after VA-ECMO decannulation	3.98 (2.62, 5.74)	4.39 (2.57, 5.69)	3.59 (2.74, 6.04)	0.88
Time from VA-ECMO decannulation to first echocardiogram after VA-ECMO decannulation	1.39 (0.78, 2.86)	1.55 (0.88, 2.42)	1.12 (0.79, 3.00)	0.91
Time to IABP removal				
Time from IABP removal to first echocardiogram after VA-ECMO decannulation	--	1.91 (1.20, 3.57)	--	--
Time from first echocardiogram after VA-ECMO decannulation to IABP removal (after decannulation)	--	1.00 (0.31, 1.23)	--	--
Vasopressor usage				
Time from ending vasopressors/inotropes (before decannulation) to first echocardiogram after VA-ECMO decannulation	4.04 (1.70, 4.69)	4.21 (2.90, 4.61)	2.88 (1.36, 4.90)	0.47
Time from first echocardiogram after VA-ECMO decannulation to ending vasopressors/inotropes (after decannulation)	0.67 (0.12, 1.64)	0.44 (0.14, 1.47)	1.45 (0.76, 1.83)	0.71

*Difference between patients with adjunctive unloading devices and patients without adjunctive unloading devices.

Table 8. Post-Hoc Comparisons for LVEF in Unloading Strategy Sensitivity Analysis.				
Post-Hoc Comparison for LVEF by Stage	**Difference (Percentage)**	**Lower Bound of 95% Confidence Interval**	**Upper Bound of 95% Confidence Interval**	**$P_{adjusted}$**
Final Turndown, Highest Flow – First Echocardiogram	16.6	9.88	23.3	**<0.001**
Final Turndown, Lowest Flow – First Echocardiogram	21.0	14.2	27.7	**<0.001**
After Decannulation – First Echocardiogram	32.6	24.9	40.3	**<0.001**
First Turndown, Highest Flow – First Echocardiogram	4.66	-4.53	13.9	0.69
First Turndown, Lowest Flow – First Echocardiogram	9.20	0.004	18.4	**0.049**
Final Turndown, Lowest Flow – Final Turndown, Highest Flow	4.36	-2.35	11.1	0.43
After Decannulation – Final Turndown, Highest Flow	16.0	8.28	23.7	**<0.001**
First Turndown, Highest Flow – Final Turndown, Highest Flow	-11.9	-21.1	-2.74	**0.003**

Table 8. Post-Hoc Comparisons for LVEF in Unloading Strategy Sensitivity Analysis.				
First Turndown, Lowest Flow – Final Turndown, Highest Flow	-7.40	-16.6	1.80	0.19
After Decannulation – Final Turndown, Highest Flow	11.6	3.91	19.3	**<0.001**
First Turndown, Highest Flow – Final Turndown, Lowest Flow	-16.3	-25.5	-7.10	**<0.001**
First Turndown, Lowest Flow – Final Turndown, Lowest Flow	-11.8	-21.0	-2.57	**0.004**
First Turndown, Highest Flow – After Decannulation	-27.9	-37.9	-18.0	**<0.001**
First Turndown, Lowest Flow – After Decannulation	-23.4	-33.3	-13.4	**<0.001**
First Turndown, Lowest Flow – First Turndown, Highest Flow	4.54	-6.60	15.7	0.85

Table 9. Post-Hoc Comparisons for Fractional Shortening in Unloading Strategy Sensitivity Analysis.				
Post-Hoc Comparison for Fractional Shortening by Stage	**Difference (Percentage)**	**Lower Bound of 95% Confidence Interval**	**Upper Bound of 95% Confidence Interval**	**$P_{adjusted}$**
First Turndown, Highest Flow – First Echocardiogram	0.030	-0.053	0.114	0.90
First Turndown, Lowest Flow – First Echocardiogram	0.032	-0.052	0.117	0.89
Final Turndown, Highest Flow – First Echocardiogram	0.064	0.004	0.124	**0.027**
Final Turndown, Lowest Flow – First Echocardiogram	0.092	0.032	0.153	**<0.001**
After Decannulation – First Echocardiogram	0.170	0.102	0.238	**<0.001**
First Turndown, Lowest Flow – First Turndown, Highest Flow	-0.0017	-0.105	0.101	>0.99
Final Turndown, Highest Flow – First Turndown, Highest Flow	0.034	-0.050	0.118	0.85
Final Turndown, Lowest Flow – First Turndown, Highest Flow	0.062	-0.023	0.146	0.29
After Decannulation –	0.139	0.049	0.229	**<0.001**

Table 9. Post-Hoc Comparisons for Fractional Shortening in Unloading Strategy Sensitivity Analysis.				
First Turndown, Highest Flow				
Final Turndown, Highest Flow – First Turndown, Lowest Flow	0.032	-0.052	0.117	0.89
Final Turndown, Lowest Flow – First Turndown, Lowest Flow	0.060	-0.026	0.145	0.34
After Decannulation – First Turndown, Lowest Flow	0.138	0.047	0.229	**<0.001**
Final Turndown, Lowest Flow – Final Turndown, Highest Flow	0.028	-0.034	0.089	0.79
After Decannulation – Final Turndown, Highest Flow	0.105	0.036	0.174	**<0.001**
After Decannulation – Final Turndown, Lowest Flow	0.077	0.008	0.147	**0.02**

Table 10. Relationship of Right Ventricular Function to Vital Status.			
Stage	**Alive** **n = 38**	**Dead** **n = 39**	**p Value**
First Echocardiogram After Rewarming			
Indeterminate	1 (2.8%)	0 (0.0%)	0.41
Normal	0 (0.0%)	1 (2.8%)	
Mildly Reduced	6 (16.7%)	7 (19.4%)	
Moderately Reduced	4 (11.1%)	8 (22.2%)	
Severely Reduced	25 (69.4%)	20 (55.6%)	
First Turndown Echocardiogram, Highest Flow			
Indeterminate	3 (18.8%)	0 (0.0%)	0.06
Normal	1 (6.3%)	1 (8.3%)	
Mildly Reduced	2 (12.5%)	3 (25.0%)	
Moderately Reduced	7 (43.8%)	1 (8.3%)	
Severely Reduced	3 (18.8%)	7 (58.3%)	
First Turndown Echocardiogram, Lowest Flow			
Indeterminate	4 (25.0%)	0 (0.0%)	0.23
Normal	2 (12.5%)	2 (16.7%)	
Mildly Reduced	4 (25.0%)	2 (16.7%)	
Moderately Reduced	4 (25.0%)	3 (25.0%)	
Severely Reduced	2 (12.5%)	5 (41.7%)	
Final Turndown Echocardiogram, Highest Flow			
Indeterminate	5 (13.2%)	7 (18.0%)	0.91
Normal	15 (39.5%)	12 (30.8%)	
Mildly Reduced	4 (10.5%)	6 (15.4%)	
Moderately Reduced	7 (18.4%)	7 (18.0%)	
Severely Reduced	7 (18.4%)	7 (18.0%)	
Final Turndown Echocardiogram, Lowest Flow			

Table 10. Relationship of Right Ventricular Function to Vital Status.			
Indeterminate	5 (13.2%)	7 (18.0%)	0.94
Normal	16 (42.1%)	13 (33.3%)	
Mildly Reduced	5 (13.2%)	6 (15.4%)	
Moderately Reduced	6 (15.8%)	6 (15.4%)	
Severely Reduced	6 (15.8%)	7 (18.0%)	
After Decannulation			
Indeterminate	2 (6.5%)	2 (12.5%)	0.18
Normal	23 (74.2%)	10 (62.5%)	
Mildly Reduced	6 (19.4%)	2 (12.5%)	
Moderately Reduced	0 (0.0%)	2 (12.5%)	
Severely Reduced	0 (0.0%)	0 (0.0%)	

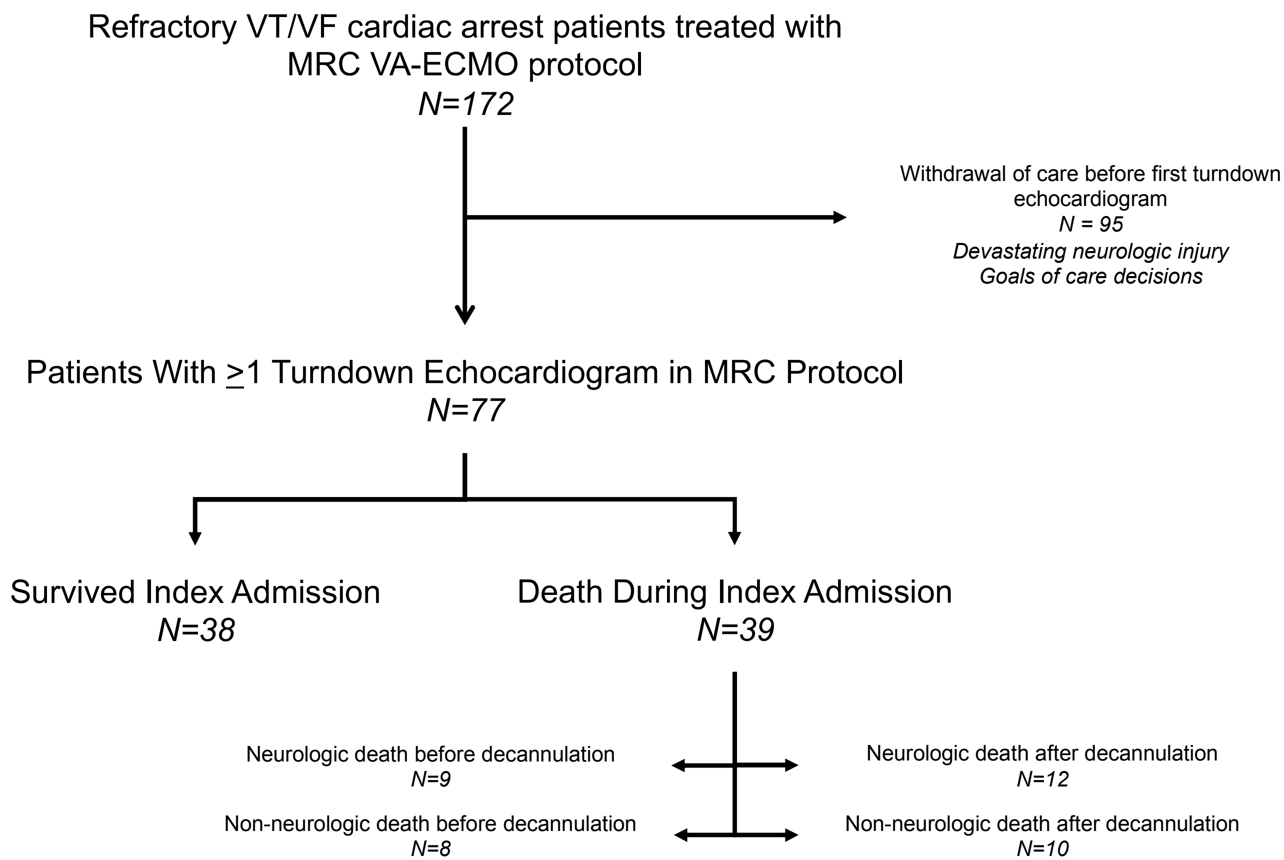

Figure 1. Flow Diagram of Refractory VT/VF Cardiac Arrest Patients Treated With VA-ECMO.

MRC = Minnesota Resuscitation Consortium; VA-ECMO = venoarterial extracorporeal membrane oxygenation; VT/VF = ventricular tachycardia/ventricular fibrillation.

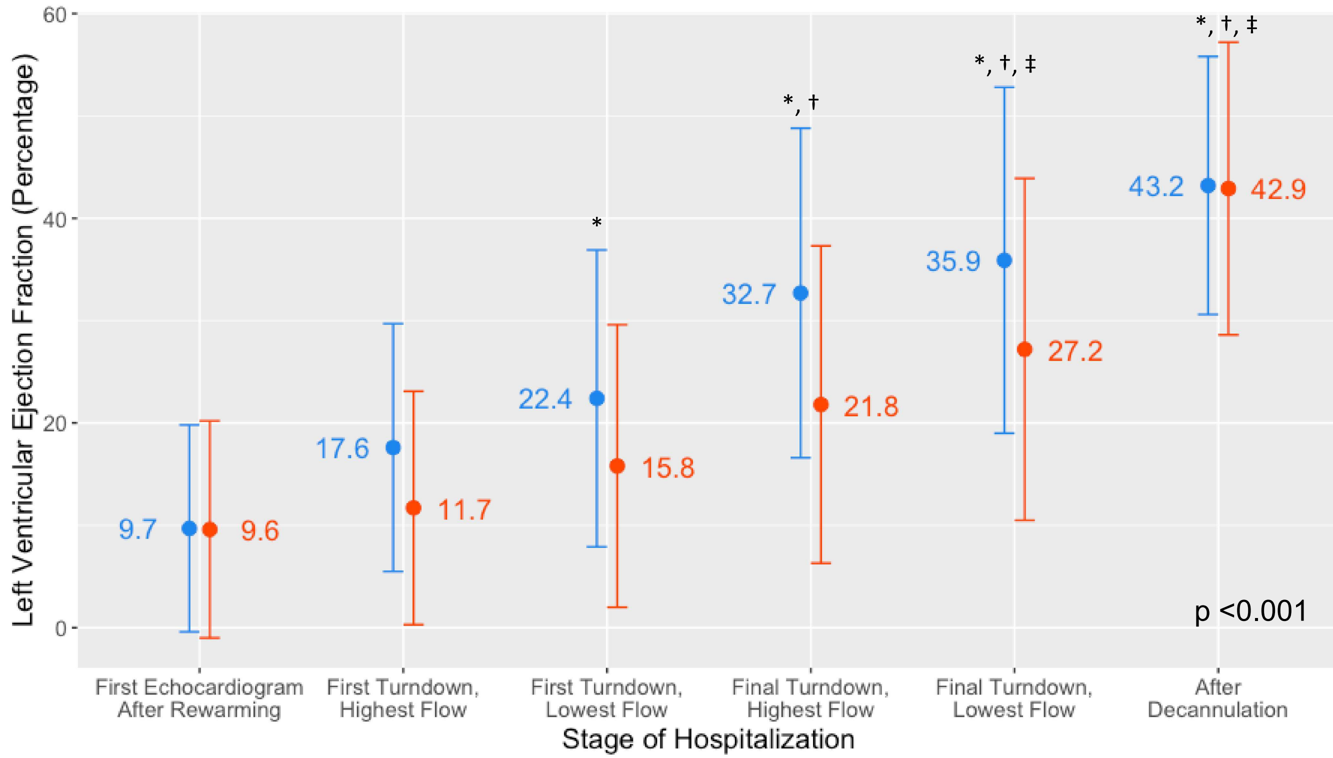

Figure 2. Change in Left Ventricular Ejection Fraction During Hospitalization.

The patients that survived to hospital discharge are represented in blue whereas as the patients that died during the index hospitalization are represented in red. * = difference from first echocardiogram. † = difference from first turndown echocardiogram, highest flow. ‡ = difference from first turndown echocardiogram, lowest flow.

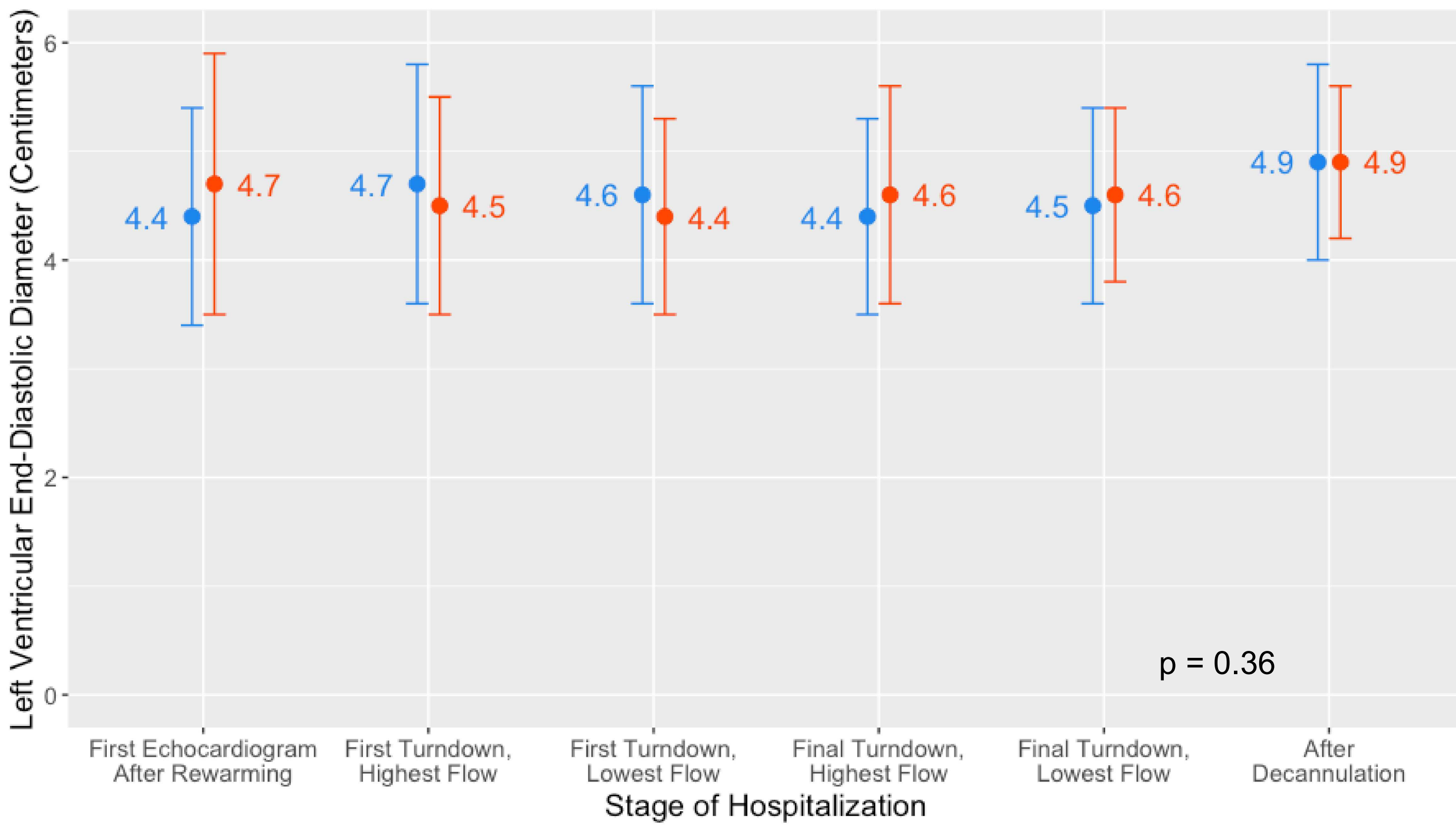

Figure 3. Change in Left Ventricular End-Diastolic Diameter During Hospitalization.

The patients that survived to hospital discharge are represented in blue whereas as the patients that died during the index hospitalization are represented in red.

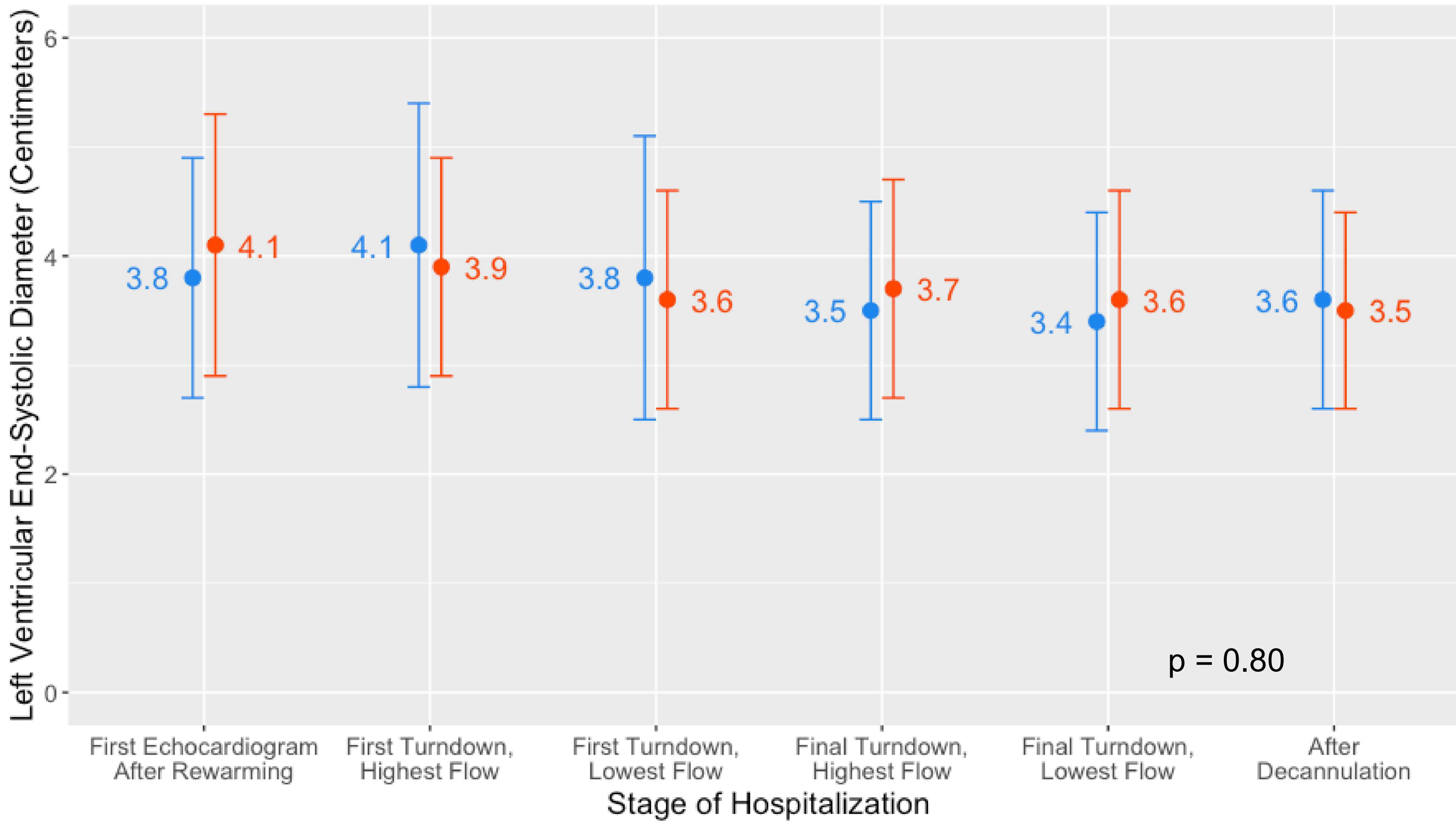

Figure 4. Change in Left Ventricular End-Systolic Diameter During Hospitalization.

The patients that survived to hospital discharge are represented in blue whereas as the patients that died during the index hospitalization are represented in red.

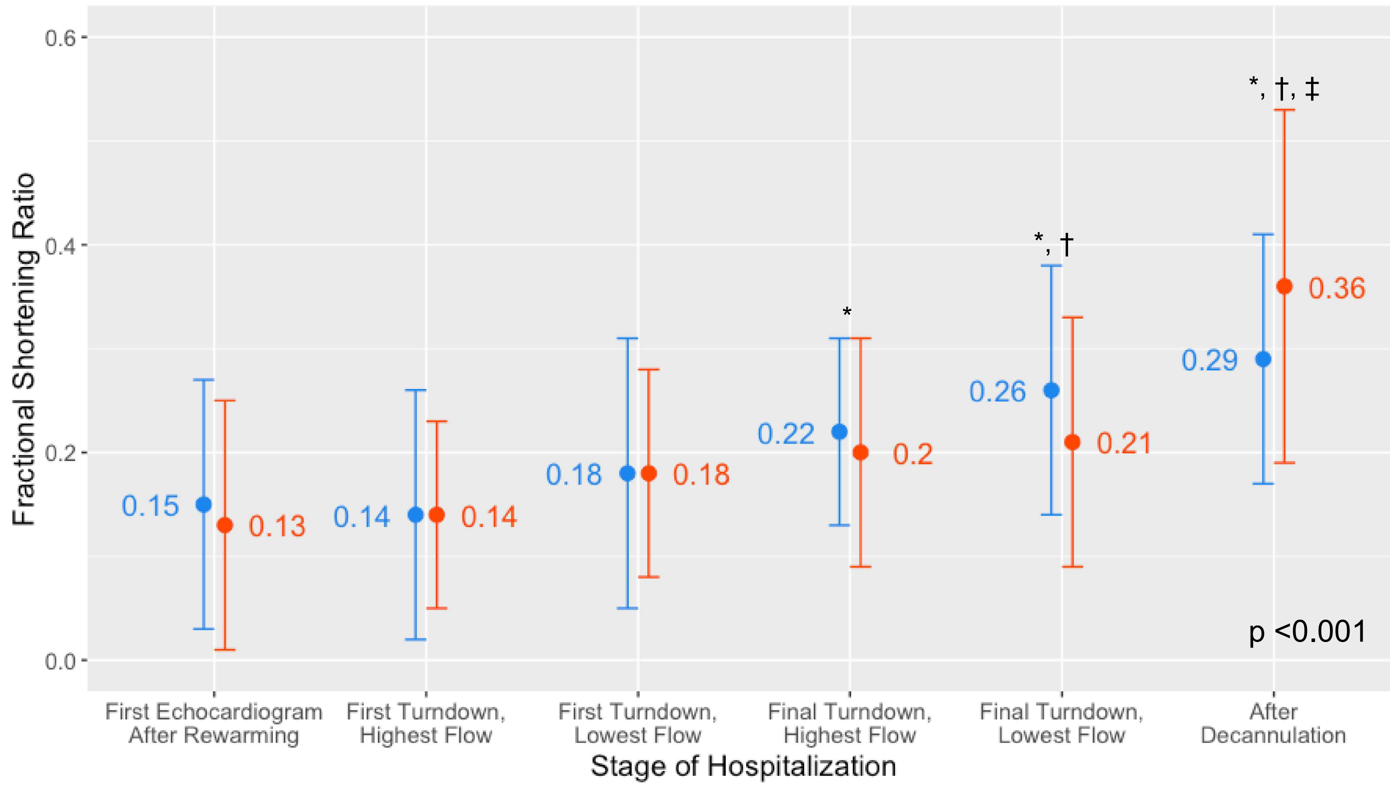

Figure 5. Change in Fractional Shortening Ratio During Hospitalization.

The patients that survived to hospital discharge are represented in blue whereas as the patients that died during the index hospitalization are represented in red. * = difference from first echocardiogram. † = difference from first turndown echocardiogram, highest flow. ‡ = difference from first turndown echocardiogram, lowest flow.