Published in final edited form as:

Crit Care Med. 2017 February ; 45(2): 225–233. doi:10.1097/CCM.0000000000002065.

Relative Bradycardia in Patients with Septic Shock Requiring Vasopressor Therapy

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Abstract

Importance—Tachycardia is common in septic shock, but many patients with septic shock are relatively bradycardic. The incidence, determinants, and implications of relative bradycardia (heart rate <80 beats/min) in septic shock are unknown.

Objective—To determine mortality associated with patients who are relatively bradycardic while in septic shock.

Design—Retrospective study of patients admitted for septic shock to study ICUs during 2005–2013.

Setting—One large academic referral hospital and two community hospitals.

Participants—Adult patients with septic shock requiring vasopressors.

Intervention—None.

Measurements—Primary outcome was 28-day mortality. We used multivariate logistic regression to evaluate the association between relative bradycardia and mortality, controlling for confounding with inverse probability treatment weighting using a propensity score.

Results—We identified 1,554 patients with septic shock, of whom 686 (44%) met criteria for relative bradycardia at some time. Twenty-eight day mortality in this group was 21% compared to 34% in the never-bradycardic group ($p < 0.001$). Relatively bradycardic patients were older (65 vs. 60 years, $p < 0.001$) and had slightly lower illness severity (SOFA 10 vs 11, $p = 0.004$, and APACHE II 27 vs. 28, $p = 0.008$). After inverse probability treatment weighting, covariates were balanced, and the association between relative bradycardia and survival persisted ($p < 0.001$).

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The remaining authors have disclosed that they do not have any potential conflicts of interest.

Conclusions—Relative bradycardia in patients with septic shock is associated with lower mortality, even after adjustment for confounding. Our data support expanded investigation into whether inducing relative bradycardia will benefit patients with septic shock.

Keywords

septic shock; bradycardia; vasopressor therapy

Introduction

Septic shock is a common, complex syndrome associated with substantial morbidity and mortality.(1–3) Patients with septic shock have an acute dysregulated systemic response to infection leading to organ dysfunction and cardiovascular compromise, generally necessitating infusions of vasopressor medications in an intensive care unit (ICU).(2, 4, 5)

Septic shock leads to impaired tissue oxygenation and perfusion, increased oxidative stress, and dysregulated inflammatory response.(5–7) In the initial phase, septic shock represents in part a hypovolemic state due to vasoplegia and capillary leak (“distributive” shock), with defects in cardiac preload and afterload related to increased capillary permeability(6) and low vascular tone.(8, 9) Tachycardia may be a compensatory response to this reduced cardiac preload to maintain cardiac output.(9) After initial treatment and fluid resuscitation, however, adrenergic over-stimulation(10) may contribute to persistence of tachycardia. Persistent tachycardia in septic shock may be associated with disruptions in cardiac function, (11) including increased myocardial oxygen consumption and impaired diastolic filling,(12, 13) as well as impairment of the baroreflex system (indicated by loss of heart rate variability).(14, 15) Observations from small cohorts suggest that tachycardia in septic shock is associated with higher mortality.(16, 17)

On the other end of the spectrum, some patients with septic shock are relatively bradycardic (18, 19) with heart rates < 80–90 beats/min. This relative bradycardia may reflect lower sympathetic and/or higher parasympathetic tone; its implications are not yet known.

We retrospectively investigated the association of relative bradycardia with mortality in septic shock, controlling for the propensity to be relatively bradycardic. We hypothesized that relative bradycardia in septic shock would be associated with lower mortality.

Materials and Methods

Patients

We identified patients with septic shock drawn from two cohorts of patients admitted to Intermountain Healthcare hospitals (Figure 1). From both cohorts, we included only adult patients admitted to ICUs with septic shock requiring vasopressor therapy. The first cohort is a subset of a quality improvement (QI) cohort(20) of septic patients admitted to a study ICU from January 2006–May 2013 (n=2,687). We included the subset of 1,353 patients with septic shock (as defined in then-current consensus guidelines(21)) receiving vasopressor infusion from the 3 study hospitals. The second cohort included patients with vasopressor-refractory shock from any cause, defined as requiring at least 1 mcg/kg/min of

norepinephrine or equivalent(22), admitted between August 1, 2005 and August 31, 2010 (n=443). Within this cohort, we studied the 201 patients for whom sepsis was the cause of shock admitted to the same 3 hospitals. Neither cohort enrolled pregnant patients. We included only the first ICU admission for each patient. We assigned the 27 patients present in both cohorts to the vasopressor-refractory shock cohort.

The Intermountain Institutional Review Board (IRB #1014318) approved this study with waiver of informed consent.

Assessment of Heart Rate

In our prespecified primary analysis, we defined relative bradycardia as heart rate < 80 beats/min, a threshold we chose because tachycardia in sepsis is often defined as a heart rate > 90–100 beats/min.(4, 19) Study ICUs electronically store 15-minute moving median values for vital signs.

Relative bradycardia was classified in three ways (see Table 1): dichotomously, extent of bradycardia, and weighted mean heart rate. For the primary, dichotomous definition, if no median heart rate exceeded the heart rate threshold for 60 minutes, the patient was considered to be bradycardic. We classified patients dichotomously as either ever-bradycardic (if they had at least one hour-long episode of bradycardia) or never-bradycardic. If a continuous bradycardic episode lasted longer than one hour, the entire period was counted as one episode. In a secondary definition, we measured extent of bradycardia by calculating the area under the curve (AUC) for heart rate <80 beats/min for each patient (see eFigure 1 in the Online Data Supplement), normalizing this area for the total time on vasopressors. Finally, we calculated the weighted mean heart rate while on vasopressors. Heart rate data was collected while patients were receiving a vasopressor infusion.

Clinical Data

Trained reviewers abstracted each subject's medical record to verify the presence and etiology of septic shock.(23, 24) We calculated Acute Physiology and Chronic Health Evaluation-II (APACHE II),(25) Sequential Organ Failure Assessment (SOFA)(26), and Elixhauser (which includes presence of hypothyroidism and diabetes mellitus) comorbidity scores.(27, 28) Presence of mechanical ventilation during admission was determined from the electronic medical record (EMR). Infusion rates of vasopressors (norepinephrine, epinephrine, dopamine, phenylephrine, and vasopressin) are automatically uploaded in real-time to hospital EMRs. We analyzed all vasopressors administered during the ICU stay, converting them to norepinephrine-equivalent dosages according to standard equivalencies(22). We also analyzed inotropic and chronotropic agents (dobutamine, isoproterenol, and milrinone) administered during the ICU stay. For each infusion, we calculated weighted mean dose, maximum dose, and total duration of administration. Weighted mean doses were normalized for the total time of infusion. The weighted mean of the mean arterial pressure (MAP) was normalized to the total time on vasopressors.

We reviewed admission electrocardiograms (ECGs) for all patients. From ECGs, we abstracted heart rate/rhythm, ischemia or infarction, and conduction abnormalities. We obtained the diagnosis of atrial fibrillation from ECGs and diagnostic codes (see Online

Data Supplement). Ejection fraction (EF) was obtained from clinical echocardiography results. Transthoracic echocardiograms were reviewed for up to one year prior to and up to 48 hours after a reference time (see Online Data Supplement). We also determined whether patients had a permanent pacemaker prior to hospital admission and whether a pacemaker was placed during the index hospitalization by chart review.

We determined whether patients were receiving atrioventricular nodal blocking medications at admission (see eList 1 in the Online Data Supplement) based on the EMR. ICU medications (see eTable 1 in the Online Data Supplement) commonly associated with incident bradycardia were recorded if a bradycardic episode occurred within three half-lives of the closest preceding medication administration.

Clinical Outcomes

Our prespecified primary outcome was 28-day all-cause mortality, determined from the Intermountain Death Record, which incorporates Utah state vital statistics. Secondary outcomes included hospital length of stay (LOS), ICU LOS, organ failure free days, and vasopressor free days. Organ failure free days were calculated using SOFA scores: days on which the SOFA organ subscore was <2 were considered to be organ-failure-free.(29)

Statistical Methods

Primary analysis—Our prespecified primary analysis was to assess the association between relative bradycardia (using the dichotomous definition, see Table 1) and 28-day mortality using logistic regression while controlling for the propensity to be bradycardic and other relevant covariates. Inverse probability of treatment weighting (IPTW) uses a propensity score to adjust for confounding in the logistic regression model.(30, 31) This method weights each patient by the inverse of the probability of being relatively bradycardic, resulting in a “pseudo” population where the distributions of covariates are independent of bradycardia. In order to more accurately estimate the variance of the parameter estimates, we stabilized the weights by the overall probability of being bradycardic. The propensity score was defined as the probability of being bradycardic based on a logistic regression model, where relevant predictors of bradycardia were identified from candidate predictors available upon admission (eTable 2) using backward stepwise selection, which minimized the Akaike information criterion (AIC). We also used the AIC-minimizing backward stepwise selection procedure to build the primary regression model of mortality (see eTable 3 for all candidate predictors). We modeled each vasopressor independently, to determine whether, e.g., phenylephrine affected both heart rate and mortality.

Secondary and sensitivity analyses—In paired secondary analyses, we repeated the propensity-adjusted regression model using the extent of bradycardia or the weighted mean heart rate while on vasopressors. We performed a sensitivity analysis excluding the last 6 hours of vasopressor infusion (when patients were presumably dying or liberating from vasopressors). In an exploratory analysis to probe the effect of vasopressor initiation on heart rate, we calculated the weighted mean heart rate for the hour prior to and the hour after vasopressor initiation and calculated the percent change in heart rate associated with the initiation of vasopressors. As a final exploratory analysis, we calculated the change in

weighted mean heart rate over the first 24 hours, which was defined as: (weighted mean HR from 0–2 hours) – (weighted mean HR from 23–25 hours), and included this variable as a candidate predictor in the propensity model for mortality.

We used effect plots to visualize the relationship between the extent of bradycardia and various outcomes. Hospital LOS, ICU LOS, organ failure-free days, and vasopressor-free days were modeled using propensity-adjusted linear regression with backward stepwise feature selection (eTable 3). A Box-Cox transformation was applied to both hospital and ICU LOS for all regression analyses. All models were adjusted to control for study hospital.

Given the potential interest in mortality at thresholds besides our prespecified threshold of 80 beats/min, we explored whether there was a heart rate threshold at which predicted probability for 28-day mortality was minimized. Using the same methodology to identify relatively bradycardic patients described above, we identified patients considered “bradycardic” using heart rates at multiple thresholds (50–140 beats/min at intervals of 5 beats/min). We determined the predicted probability of 28-day mortality, adjusted for admission APACHE II score, at each heart rate threshold.

To limit the risk of Type 1 error, we limited false discovery rate (FDR) to 5%.⁽³²⁾ All analyses were conducted using the R Statistical Package, version 3.1.2.⁽³³⁾

Results

We identified a total of 1,554 patients (Figure 1), of whom 686 (44%) were ever bradycardic. Admission characteristics for ever-bradycardic and never-bradycardic patients are displayed in Table 2 (see also eTable 4 in Online Data Supplement). Bradycardic patients were older and had slightly lower APACHE II and SOFA scores than never-bradycardic patients. Total Elixhauser scores were similar, though bradycardic patients were more likely to have hypothyroidism.

Results of Primary Analysis

Overall 28-day mortality was 28% (n=435). Mortality was significantly lower in the bradycardic group than in the never-bradycardic group (21% vs. 34%, $p<0.001$). The results of the primary propensity-adjusted regression analysis of 28-day mortality are displayed in Table 3. Bradycardia was associated with significantly lower mortality (OR=0.55, adjusted $p<0.001$). In the propensity model, predictors of bradycardia included age, admission APACHE II, hypothyroidism, diabetes, presence of nodal blockers at admission and increased PR interval. See eTable 2 for the full propensity model. Covariate balance was achieved in the inverse probability of treatment weighted sample (see eTable 5).

Results of Secondary Analyses

The extent of bradycardia (normalized AUC of HR <80 beats/min) was also associated with significantly lower mortality, as depicted in Figure 2 (OR 0.92 per beats/min, adjusted $p<0.001$). Weighted mean heart rate was also significantly associated with mortality, where lower mean heart rates were associated with lower mortality (OR 1.03 per beats/min, $p<0.001$), see Figure 2. In a sensitivity analysis excluding the last 6 hours of vasopressor

data, the association between mortality and the extent of bradycardia was unchanged (OR 0.92 per beats/min, adjusted $p < 0.001$). We found that the median change in heart rate from the hour before to the hour after initiation of vasopressors was small: median change was -1.0% (IQR: -5.1% , 3.3%). The change in heart rate for bradycardic patients was slightly, but significantly, lower than for never-bradycardic patients (median -1.4% [95% CI: -2.1% , -0.9%] vs. median -0.8% [95% CI: -1.0% , 0.0%], $p = 0.004$). Weighted mean heart rate change over the first 24 hours of septic shock was 6 (SD 18) beats/min and, when included as a candidate predictor in the logistic regression, was associated with lower mortality (OR 0.99, $p = 0.005$).

Our exploratory analysis of the association between APACHE II-adjusted mortality and various heart rate thresholds, is displayed in Figure 3. Visually, severity-adjusted mortality appeared to reach a nadir around 80 beats/min.

Bradycardia (dichotomous) was associated with 2.1 more organ failure free days to day 28, after controlling for covariates ($p < 0.001$). Organ failure free days increased as extent of bradycardia increased ($p < 0.001$). Days free of specific (renal, cardiovascular and respiratory) organ failures were also higher in bradycardic patients.

Bradycardia (dichotomous) was also associated with a 0.55 ($p = 0.03$) increase in vasopressor-free days, after adjusting for covariates. Vasopressor-free days also increased ($p = 0.001$) as extent of bradycardia increased. Relative bradycardia was not a significant predictor of hospital or ICU LOS.

While all patients received vasopressors, the distribution of individual vasopressors differed between bradycardic and never-bradycardic patients (see eTable 4 in Online Data Supplement). Bradycardic patients had lower mean vasopressor infusion rates (norepinephrine equivalent doses 0.10 mcg/kg/min vs. 0.13 mcg/kg/min, $p = 0.004$), but for longer duration (31 hours vs. 20 hours, $p < 0.001$). The maximum dose of vasopressors did not differ between the groups ($p = 0.31$). Never-bradycardic patients more frequently received dobutamine infusions. The weighted mean of the MAP was the same for both groups (73 mmHg vs 72 mmHg, $p = 0.52$).

Bradycardic patients were more likely to be taking a nodal-blocking agent on admission (37% vs 26%, $p < 0.001$), but this was not a relevant predictor in the primary regression model of mortality. Of the bradycardic patients, 364 (52%) received medications that commonly induce bradycardia within three half-lives of the beginning of episodes of relative bradycardia. Relatively bradycardic patients who received bradycardia-inducing medications had a similar or lower mortality than never-bradycardic patients who received bradycardia-inducing medications (eTable 1).

Admission ECG data was available for 85% of patients. QRS duration and PR interval were both slightly longer in bradycardic patients; QTc did not differ. Presence of chronic atrial fibrillation was not significant in the primary regression model. An echocardiogram was available for review in 1,223 (79%) patients. EF was similar among relatively bradycardic and never-bradycardic patients (mean 57% vs. 54%, $p = 0.05$). Among bradycardic patients,

there was no significant difference in mortality between patients with and without a pacemaker present at admission ($p=0.16$). (See Online Data Supplement for further results.)

Discussion

In this large cohort of patients with septic shock, relative bradycardia was both common and associated with significantly higher survival, even after control for multiple covariates and the propensity to be relatively bradycardic. The association was robust with several definitions of relative bradycardia and multiple sensitivity analyses. Secondary outcomes, such as organ failure-free and vasopressor-free days, tracked the mortality outcomes.

While earlier studies have suggested that sustained tachycardia is toxic in septic shock(16, 34), our study improves upon prior observations in terms of its size, the use of propensity adjustment to minimize the effect of confounding, and the exploration of lower heart rates to include relative bradycardia.

Although it is plausible that bradycardia may simply be a surrogate for decreased disease severity and lower doses of vasopressors, our propensity adjustment suggests that such is not the case. Even after controlling for severity of illness, vasopressor infusions, comorbidities and the probability of being bradycardic, relative bradycardia was strongly associated with higher survival.

The apparent association between relative bradycardia and mortality could be explained via multiple mechanisms. A promising possible mechanism appears to be the deleterious effect of adrenergic over-stimulation, of which tachycardia persisting after volume expansion is an important marker. Additionally, bradycardia might improve outcomes by decreased cardiac work and increased coronary artery perfusion.(35) While chronotropic incompetence has been associated with increased mortality in older patients,(36) our results suggest that such a phenomenon is not relevant in septic shock.

Optimal thresholds for induced bradycardia are not well defined, and our results suggest the possibility that the survival effect appears to level off at heart rates below 80. We selected a threshold of 80 *a priori* rather than a more extreme threshold, such as 50 or 60 beats/min, to decrease the possibility that bradycardia was the cause of shock rather than a marker of sympathovagal balance. Similar observations have motivated attempts to slow heart rate by administration of adrenergic antagonists (“beta-blockers”) during septic shock.(37–40) Such efforts should be undertaken with caution; past studies with a goal of correcting physiologic parameters, such as oxygen delivery, to “normal” levels have rarely improved mortality and may be toxic.(41–43)

Several factors were associated with bradycardia in our population, including advancing age, lower APACHE II score, hypothyroidism, diabetes, presence of a nodal blocker at admission, and mild conduction abnormalities. We could not formally distinguish well-treated hypothyroidism from myxedema coma, though the latter is rare. Hypothyroidism was a predictor of bradycardia, but it did not predict mortality. While more patients who were on nodal blockers prior to admit were bradycardic during their admission, this also did not predict mortality. Partially controlled data from an Italian registry suggested that pre-

admission beta blocker use may be associated with better outcomes.(44) Our study does not support this finding; larger (ultimately prospective) studies will be required to answer that question definitively.

Our study was limited by its retrospective, observational design. The most recent definition of septic shock includes presence of an elevated lactate level as well as vasopressor administration after adequate fluid resuscitation.(2) The retrospective design of this study did not allow for collection of data on these additional parameters that may have influenced outcomes, such as details regarding fluid resuscitation, time to antibiotic administration, and lactate clearance. While inverse probability of treatment weighting for propensity adjustment limits the influence of confounding, residual confounding may still have affected our findings. And, as always, our non-randomized data may identify correlation rather than causation.

Conclusions

We studied more than 1,500 patients with septic shock on vasopressors and compared outcomes between patients with or without at least one episode of relative bradycardia (heart rate < 80 beats/min). Such relative bradycardia was associated with improved 28-day mortality. Our results provide further support for clinical equipoise in investigations of induced relative bradycardia for patients with septic shock.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank Robert Paine, III MD for close reading of the manuscript.

Source of Funding This study was funded by National Institute of General Medical Sciences (1K23GM094465 to SMB) and the Intermountain Research and Medical Foundation. The Intermountain Institutional Review Board approved this study with waiver of informed consent.

Copyright form disclosures: Dr. Talmor received support for article research from the National Institutes of Health (NIH). His institution received funding from the NHLBI, Gordon and Betty Moore Foundation, and Intensix.

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Figure 1.
Study Flow Chart

Figure 2.
Effect Plot for Bradycardia and Mortality

Predicted Probability of Mortality for Various Thresholds of Bradycardia

Figure 3.
Predicted Probability of 28-day Mortality for Various Heart rate Thresholds

Table 1

Complementary methods of assessing relative bradycardia

Term	Definition
Dichotomous (Bradycardic or not bradycardic)	Patient had a heart rate <80 beats/min for at least one hour while on vasopressors
Extent of Bradycardia (Area Under the Curve or AUC)	Sum of the time with heart rate < 80 beats/min, weighted by the distance below 80 beats/min and normalized for total time on vasopressors. See eFigure 1 for visual depiction.
Mean heart rate	Weighted mean of all measured heart rates while on vasopressors

Table 2

Patient Characteristics and Outcomes

Characteristic	Overall (n=1,554)	Ever Bradycardic (n=686)	Never Bradycardic (n=868)	p-value*
Demographics				
Age; median (IQR)	63 (51 – 74)	65 (55 – 76)	60 (49 – 72)	<0.001
Female; n (%)	801 (52%)	358 (52%)	443 (51%)	0.80
QI Cohort; n (%)	1,353 (87%)	628 (92%)	725 (84%)	<0.001
Race/ethnicity; n (%)				0.91
American Indian or Alaska Native	10 (1%)	3 (<1%)	7 (1%)	
Asian	19 (1%)	8 (1%)	11 (1%)	
Black or African American	20 (1%)	9 (1%)	11 (1%)	
Hispanic/Latino	84 (5%)	33 (5%)	51 (6%)	
Native Hawaiian or Other Islander	26 (2%)	10 (1%)	16 (2%)	
White	1,317 (85%)	591 (86%)	726 (84%)	
Unknown/Declined to respond	78 (5%)	32 (5%)	46 (5%)	
Sepsis cause; n (%)				0.36
Pneumonia	578 (37%)	236 (34%)	342 (39%)	
Urinary	335 (22%)	166 (24%)	169 (19%)	
Abdominal	185 (12%)	73 (11%)	112 (13%)	
Uncertain etiology	149 (10%)	64 (9%)	85 (10%)	
Soft Tissue	141 (9%)	70 (10%)	71 (8%)	
Bacteremia	75 (5%)	37 (5%)	38 (4%)	
Biliary	33 (2%)	13 (2%)	20 (2%)	
Endocarditis	25 (2%)	13 (2%)	12 (1%)	
Other identified etiology	15 (1%)	6 (1%)	9 (1%)	
Joint	13 (1%)	6 (1%)	7 (1%)	
Central Nervous System	5 (<1%)	2 (<1%)	3 (<1%)	
Illness Severity and Comorbidities				
Admission APACHE II score; mean $\pm$ SD	27 $\pm$ 10	27 $\pm$ 9	28 $\pm$ 10	0.008
Admission SOFA score; mean $\pm$ SD	10 $\pm$ 4	10 $\pm$ 3	11 $\pm$ 4	0.004
Mechanical Ventilation; n (%)	813 (52%)	333 (49%)	480 (55%)	0.02
Elixhauser Total; mean $\pm$ SD	5 $\pm$ 2	5 $\pm$ 2	5 $\pm$ 2	0.13
CHF; n (%)	403 (26%)	195 (28%)	208 (24%)	0.09
Diabetes; n (%)	538 (35%)	238 (35%)	300 (35%)	0.99
Hypothyroidism; n (%)	304 (20%)	170 (25%)	134 (15%)	<0.001
Cardiovascular Function				
MAP (weighted mean); mean $\pm$ SD	72 $\pm$ 6	73 $\pm$ 6	72 $\pm$ 7	0.52
Pacemaker (on admit); n (%)	112 (7%)	69 (10%)	43 (5%)	0.001
Atrial Fibrillation; n (%)				<0.001
Never	1059 (68%)	431 (63%)	628 (72%)	
Acute	203 (13%)	104 (15%)	99 (11%)	

Characteristic	Overall (n=1,554)	Ever Bradycardic (n=686)	Never Bradycardic (n=868)	p-value*
Chronic	292 (19%)	151 (22%)	141 (16%)	
Nodal blockers (on admit); n (%)	475 (31%)	251 (37%)	224 (26%)	<0.001
Anti-arrhythmic; n (%)	52 (3%)	29 (4%)	23 (3%)	0.17
Calcium channel blocker; n (%)	76 (5%)	37 (5%)	39 (4%)	0.58
Beta blocker; n (%)	364 (23%)	195 (28%)	169 (19%)	<0.001
Digoxin; n (%)	53 (3%)	33 (5%)	20 (2%)	0.02
Hemoglobin				
Admission; mean $\pm$ SD	11.5 $\pm$ 2.5	11.4 $\pm$ 2.5	11.5 $\pm$ 2.4	0.41
At Vasopressor Initiation; mean $\pm$ SD	11.0 $\pm$ 2.2	11.0 $\pm$ 2.2	11.0 $\pm$ 2.3	0.97
Outcomes				
28-day Mortality; n (%)	435 (28%)	143 (21%)	292 (34%)	<0.001
Hospital LOS; median (IQR)	7 (4 – 13)	7 (4 – 14)	6 (3 – 12)	<0.001
ICU LOS; median (IQR)	4.3 (2.4 – 9.2)	4.8 (2.8 – 11.0)	3.9 (2.0 – 8.2)	<0.001
28-day OFFD Overall; median (IQR)	21 (0 – 25)	22 (2 – 26)	20 (0 – 25)	0.001
14-day Vasopressor free days; median (IQR)	12 (5 – 13)	12 (9 – 13)	12 (0 – 13)	0.89

* p-values adjusted using the false discovery rate (5%)

IQR= interquartile range, QI= Quality Improvement, APACHE II= Acute Physiologic Assessment and Chronic Health Evaluation, SOFA= Sequential Organ Failure Assessment, CHF = congestive heart failure, MAP= mean arterial pressure, SD= standard deviation, LOS= length of stay, ICU = Intensive Care Unity, OFFD= organ failure free days

Table 3

Primary Multivariable Logistic Regression for 28-day Mortality

Variable	Odds Ratio	95% Confidence Interval	p-value
Bradycardia (HR < 80)	0.545	(0.392, 0.754)	<0.001
Age	1.041	(1.028, 1.054)	<0.001
Female	0.766	(0.558, 1.051)	0.100
Atrial Fibrillation (Acute)	1.004	(0.637, 1.566)	0.987
Atrial Fibrillation (Chronic)	1.435	(0.959, 2.141)	0.077
Mechanical Ventilation	2.778	(1.937, 4.010)	<0.001
MAP (weighted mean, per 1 mmHg increase)	0.924	(0.896, 0.951)	<0.001
Hemoglobin (at vasopressor start)	0.924	(0.861, 0.991)	0.027
NEE weighted mean dose (per 0.01 mcg/kg/min increase)	1.040	(1.030, 1.050)	<0.001
NEE total duration (per 1 hour increase)	1.002	(1.000, 1.005)	0.050
Received Phenylephrine	0.590	(0.370, 0.932)	0.025
Received Epinephrine	2.265	(1.302, 3.954)	0.004
Dobutamine maximum dose (per 1 mcg/kg/min increase)	1.043	(0.996, 1.092)	0.072
Milrinone total duration (per 1 hour increase)	0.994	(0.982, 1.000)	0.162
Sepsis cause (UTI or skin)	0.598	(0.411, 0.861)	0.006
QRS Duration	0.994	(0.987, 1.000)	0.060

HR = Heart Rate, MAP= mean arterial pressure, NEE= Norepinephrine equivalent, UTI = Urinary Tract Infection