EDITORIAL

Is There a Role for β-Blockade in Septic Shock?

Michael R. Pinsky, MD

Single-cell and multicell organisms have developed elaborate networks to minimize injury, repair damage, and fend off invasion by other organisms[1] with the goal of maximizing the probability of surviving overwhelming stress. These networks in higher organisms were described by Walter Cannon[2] as the acute stress response. The acute stress response includes centrally mediated sympathetic neural and humoral activation, increased vascular smooth muscle tone, catecholamine and cortisol release into the bloodstream, minimized pain perception, altered intercellular and intracellular signaling and intermediary metabolism, and a proinflammatory, prothrombotic intravascular state.

The clinical and physiologic manifestations of these responses include increased cardiac inotropy, peripheral vasoconstriction (although some vascular beds may be vasodilated), and tachycardia. Such manifestations, although intended to be helpful in the short term, may become detrimental if they persist. This detrimental reaction is well described for chronic conditions like low-output heart failure. In that state, the body responds by assuming that the low output is due to hypovolemia. Thus, the physiologic response is fluid retention and increased vasomotor tone.[3] Hence, there is therapeutic benefit from afterload-reduction agents, β-adrenergic blockers, and diuretics.[4] Long-term β-blockade of patients with coronary artery disease improved survival in patients at risk of sudden death, but only if the heart rate was controlled,[5] presumably because that level of β-blockade has a measurable physiologic effect. The improved outcomes among these patients resulted from a marked reduction in sudden death due to a slower progression of coronary artery disease and less tendency for malignant arrhythmias.[6]

Related article

Based on this logic, Morelli et al[7] hypothesized that, because patients in septic shock had many of the manifestations of a hyperadrenergic response, pharmacologic reduction in β-adrenergic tone may be beneficial if patients were appropriately resuscitated. In this issue of *JAMA*, these investigators report the results of a single-center randomized clinical trial designed to measure the effects of the short-acting β-blocker, esmolol, in septic shock. The authors randomized 154 patients to receive esmolol (n = 77) or usual care (n = 77), and using sinoatrial adrenergic sensitivity as a barometer of adequate β-blockage,[5] titrated esmolol to maintain the heart rate between 80/min and 94/min.

Because patients with sepsis have a wide range of sympathetic activation and responsiveness, giving a fixed dose of a β-blocker would probably be less effective and potentially harmful if given to all patients. Furthermore, because adrenergic stress persists as long as the external stress (eg, infection or injury), treatment was continued for the entire intensive care unit stay. The choice of using a short-acting β-blocker in patients requiring vasopressor therapy to maintain organ perfusion pressure was reasonable because β-blockade allows unrestricted α-adrenergic stimulation, minimizing the potential for worsening hypotension, while allowing its dosage to be accurately titrated up or down to effect.

The intervention was associated with a number of cardiac effects. First, heart rate was lowered successfully to the target range without unwanted hypotension. Second, stroke work index and left ventricular stroke work improved, presumably because of improved diastolic filling with lower heart rate. Third, overall, because the heart became more efficient (better stroke work), cardiac index and systemic oxygen delivery only decreased minimally despite the relatively large decrease in heart rate. Beyond the primary cardiac effects, there were notable improvements in the norepinephrine and fluid requirements and in arterial lactate levels in the esmolol group compared with the control group. Perhaps most surprisingly, the 28-day mortality was considerably lower in the esmolol group than in the control group (49.4% vs 80.5%; $P < .001$).

These data are consistent with selective blockage of β-adrenergic hyperactivity causing improved myocardial performance and decreased metabolic demand without compromising peripheral vascular function. Indeed, the Pao_2 to Fio_2 ratio also decreased, presumably due to decreased β-adrenergic pulmonary vasodilation causing better V̇/Q matching. Although these findings are potentially important, caution needs to be stressed before applying these results to all patients in septic shock. The reasons for this caution involve the limitations of this study and limitations in the current understanding of how β-blocker therapy can cause such effects.

The study was a single-center open-label trial. Clearly, it would be difficult to mask heart rate titration because placebo would have little effect on heart rate other than to cause a large degree of fluid resuscitation. A large multicenter clinical trial is warranted to confirm these preliminary findings. Second, more than half of the septic shock candidates for this trial were excluded because they did not have tachycardia. It is unclear whether tachycardia is the right method to identify patients in septic shock who might benefit from β-blockers. β-Blockade may be beneficial in patients with lower heart rate, and the effects may be neither due to nor proportional to the degree of sinoatrial node blockade. Third, because outpatient use of β-blockers is common, it is unknown how such patients, who were excluded from the trial, might have fared.

The mechanism by which esmolol might have improved outcome is unclear. There were no differences between the esmolol and placebo groups in rates of hepatic, renal, or myocardial injury. In a previously published pilot study on a subset of these patients, there was no measurable change in sublingual microcirculatory flow between the esmolol and control groups.[8] β-Blockers are also not without risk. The initial enthusiasm of giving all patients after myocardial infarction and surgery β-blockers to minimize the risk of postevent or postoperative myocardial infarction[9] was diminished by the findings of worsening pulmonary obstructive disease and cardiac function in many patients.[10] It is possible that patients surviving severe sepsis would have similar problems.

The findings reported by Morelli et al generate interesting questions regarding the potential role of β-blockers in the treatment of septic shock. Use of β-blockers decreases adrenergic-stimulated increased myocardial metabolic rate. Sepsis is associated with myocardial necrosis[11] and elevated troponin levels.[12] Thus, esmolol-induced reductions in metabolic stress could potentially minimize subclinical myocardial injury. This mechanism could be assessed in prospective trials with myocardial positron emission tomography, tissue Doppler imaging, or even endomyocardial biopsies to measure cardiomyocyte function. In addition, β-blockers could modulate the immune response and may improve clearance of bacteria and foreign material from the circulation, possibly leading to more rapid resolution of the septic immune dysfunctional state. This mechanism could be assessed through monitoring of the rate of blood sterilization, inflammatory load, and functional measures of immunocyte activation and responsiveness. Animal models of chronic sepsis could be used to identify parameters to follow in subsequent clinical trials.

Finally, the β-adrenergic response is multidimensional and protean. Thus, as with other therapies, such as statins, clinicians may not fully understand the reasons β-blockers improve outcome, if indeed they do. But first, it will be important to define the patients for whom use of β-blockers is most indicated and those for whom these medications should be avoided.

ARTICLE INFORMATION

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Preliminary Communication | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Heart Rate Control With Esmolol on Hemodynamic and Clinical Outcomes in Patients With Septic Shock
A Randomized Clinical Trial

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IMPORTANCE β-Blocker therapy may control heart rate and attenuate the deleterious effects of β-adrenergic receptor stimulation in septic shock. However, β-Blockers are not traditionally used for this condition and may worsen cardiovascular decompensation related through negative inotropic and hypotensive effects.

OBJECTIVE To investigate the effect of the short-acting β-blocker esmolol in patients with severe septic shock.

DESIGN, SETTING, AND PATIENTS Open-label, randomized phase 2 study, conducted in a university hospital intensive care unit (ICU) between November 2010 and July 2012, involving patients in septic shock with a heart rate of 95/min or higher requiring high-dose norepinephrine to maintain a mean arterial pressure of 65 mm Hg or higher.

INTERVENTIONS We randomly assigned 77 patients to receive a continuous infusion of esmolol titrated to maintain heart rate between 80/min and 94/min for their ICU stay and 77 patients to standard treatment.

MAIN OUTCOMES AND MEASURES Our primary outcome was a reduction in heart rate below the predefined threshold of 95/min and to maintain heart rate between 80/min and 94/min by esmolol treatment over a 96-hour period. Secondary outcomes included hemodynamic and organ function measures; norepinephrine dosages at 24, 48, 72, and 96 hours; and adverse events and mortality occurring within 28 days after randomization.

RESULTS Targeted heart rates were achieved in all patients in the esmolol group compared with those in the control group. The median AUC for heart rate during the first 96 hours was −28/min (IQR, −37 to −21) for the esmolol group vs −6/min (95% CI, −14 to 0) for the control group with a mean reduction of 18/min ($P < .001$). For stroke volume index, the median AUC for esmolol was 4 mL/m^2 (IQR, −1 to 10) vs 1 mL/m^2 for the control group (IQR, −3 to 5; $P = .02$), whereas the left ventricular stroke work index for esmolol was 3 mL/m^2 (IQR, 0 to 8) vs 1 mL/m^2 for the control group (IQR, −2 to 5; $P = .03$). For arterial lactatemia, median AUC for esmolol was −0.1 mmol/L (IQR, −0.6 to 0.2) vs 0.1 mmol/L for the control group (IQR, −0.3 for 0.6; $P = .007$); for norepinephrine, −0.11 µg/kg/min (IQR, −0.46 to 0.02) for the esmolol group vs −0.01 µg/kg/min (IQR, −0.2 to 0.44) for the control group ($P = .003$). Fluid requirements were reduced in the esmolol group: median AUC was 3975 mL/24 h (IQR, 3663 to 4200) vs 4425 mL/24 h (IQR, 4038 to 4775) for the control group ($P < .001$). We found no clinically relevant differences between groups in other cardiopulmonary variables nor in rescue therapy requirements. Twenty-eight day mortality was 49.4% in the esmolol group vs 80.5% in the control group (adjusted hazard ratio, 0.39; 95% CI, 0.26 to 0.59; $P < .001$).

CONCLUSIONS AND RELEVANCE For patients in septic shock, open-label use of esmolol vs standard care was associated with reductions in heart rates to achieve target levels, without increased adverse events. The observed improvement in mortality and other secondary clinical outcomes warrants further investigation.

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Editorial

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Septic shock is associated with excessive sympathetic outflow, high plasma catecholamine levels, myocardial depression, vascular hyporeactivity, and autonomic dysfunction.[1,2] Typically, patients have a low resistance, high-cardiac output circulation with tachycardia and arterial hypotension that may be poorly or even nonresponsive to exogenous catecholamine vasopressors. Although norepinephrine is the current recommended mainstay of treatment for sepsis-related hypotension,[3] excessive adrenergic stress has multiple adverse effects including direct myocardial damage (eg, Takotsubo [stress] cardiomyopathy and tachyarrhythmias), insulin resistance, thrombogenicity, immunosuppression, and enhanced bacterial growth.[4,5] High plasma catecholamine levels, the extent and duration of catecholamine therapy, and tachycardia are all independently associated with poor outcomes in critically ill patients.[2,6-8]

High sympathetic stress is also implicated in sepsis-induced myocardial depression.[9] Patients with sepsis often remain tachycardic, even after excluding common causes such as hypovolemia, anemia, agitation, and drug effects. β-Adrenergic blockade may enable heart rate control and limit adverse events related to sympathetic overstimulation.[5] In animal models of sepsis, β-blockade appears beneficial, particularly when given as pretreatment.[10,11] Although heart rate control is likely to improve cardiovascular performance,[9] concerns that β-blocker therapy in human septic shock may lead to cardiovascular decompensation must be considered. A good safety profile was reported in patients in septic shock who were given oral metoprolol to achieve heart rates of less than 95/min[12]; however, intravenous β-blocker therapy has not been formally investigated.

We hypothesized that intravenous β-blockade titrated to achieve heart rate control in septic shock represents an effective approach to enhance myocardial function and improve outcome without increased complications. The present study aimed to determine whether the short-acting intravenous β_1-adrenoreceptor blocker, esmolol, could reduce heart rate to be lower than a predefined threshold and measured subsequent effects on systemic hemodynamics, organ function, adverse events, and 28-day mortality.

Methods

Patients

After approval by the local institutional ethics committee, we performed the study in the 18-bed multidisciplinary intensive care unit (ICU) of the University of Rome "La Sapienza" Hospital, after written informed consent from the patients' next of kin. Enrollment occurred between November 2010 and July 2012. Inclusion criteria were the presence of septic shock requiring norepinephrine to maintain a mean arterial pressure (MAP) of 65 mm Hg or higher despite appropriate volume resuscitation (pulmonary arterial occlusion pressure ≥12 mm Hg and central venous pressure ≥8 mm Hg),[4] and a heart rate of 95/min or higher.

Exclusion criteria were age younger than 18 years, β-blocker therapy prior to randomization, pronounced cardiac dysfunction (ie, cardiac index ≤2.2 L/min/m^2 in the presence of a pulmonary arterial occlusion pressure >18 mm Hg), significant valvular heart disease, and pregnancy.

All patients were sedated with sufentanil and propofol and received mechanical ventilation using a volume-controlled mode with targeted tidal volumes of 6 mL/kg or less of predicted body weight.

Hemodynamics, Global Oxygen Transport, and Acid-Base Balance

Systemic hemodynamic monitoring included pulmonary artery catheterization (7.5F catheter, Edwards Lifesciences) and a radial artery catheter. MAP, central venous, mean pulmonary arterial, and occlusion pressures were measured at end-expiration. We monitored heart rate and ST segments continuously by electrocardiography. We measured cardiac index using the continuous thermodilution technique (Vigilance II, Edwards Lifesciences). We sampled arterial and mixed-venous blood intermittently for blood gas analyses to determine oxygen tensions and saturations, carbon dioxide tensions, pH, standard bicarbonate, and base excess. Left and right ventricular stroke work, oxygen delivery, consumption indexed to body surface area, and oxygen extraction ratios were calculated using standard formulae.

We analyzed arterial blood samples for lactate, standard hematology, biochemistry, kidney and liver function, coagulation profile tests, amylase, lipase, antithrombin, cardiac troponin I, creatine kinase MB isoenzyme (CK-MB), and C-reactive protein.

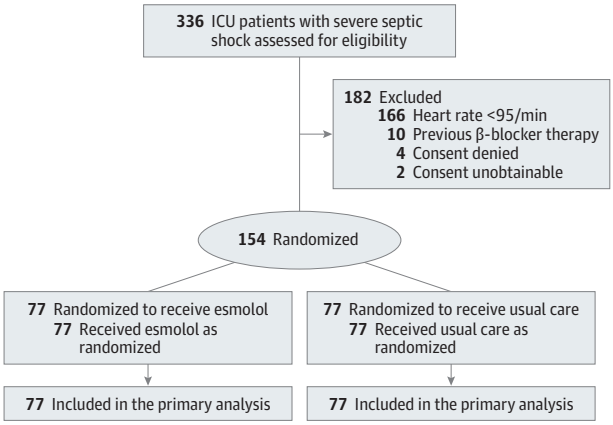
Study Design

We designed the present study as a single-center, open-label, randomized 2-group phase 2 trial. Our primary outcome was to determine whether esmolol could reduce heart rates to be lower than the predefined threshold of 95/min and to maintain heart rate between 80/min and 94/min for the duration of the patients' ICU stay. Secondary outcomes included the effect of esmolol on norepinephrine requirements, cardiorespiratory and oxygenation indices, safety end points (including markers of organ function and injury and rescue therapy with other drugs), and 28-day overall survival.

After 24 hours of hemodynamic optimization aimed at establishing an adequate circulating blood volume (adjudged by pulmonary artery occlusion pressure of ≥12 mm Hg and central venous pressures of ≥8 mm Hg), a mixed venous oxygen saturation higher than 65% and a MAP of 65 mm Hg or higher,[4] we enrolled patients if they were still requiring norepinephrine and their heart rate persisted at 95/min or higher. Patients were randomly assigned by a computer-based random-number generator to receive conventional management with or without a continuous esmolol infusion titrated to maintain heart rate between 80/min and 94/min (see eMethods in the Supplement for additional details on randomization procedures).

The esmolol infusion commenced at 25 mg × h^{-1} and progressively increased the rate at 20-minute intervals in increments of 50 mg × h^{-1}, or more slowly at the discretion of the

Figure 1. Flow Chart



ICI indicates intensive care unit.

investigators, to reach the predefined threshold rate within 12 hours. We continued infusing esmolol to maintain the predefined heart rate threshold until either ICU discharge or death with an upper dose limit of 2000 mg × h^{-1}. Participant study flow data are presented in **Figure 1**.

During the first 96 hours of the intervention period, we gave fluid challenges, as necessary, to maintain filling pressures as described above. We transfused packed red blood cells when hemoglobin concentrations decreased to less than 7 g/dL^{-1}, or if the patient exhibited clinical signs of inadequate systemic oxygen supply.[4] We titrated norepinephrine to maintain MAP of 65 mm Hg or higher and gave all patients intravenous hydrocortisone (300 mg/d^{-1}) as a continuous infusion. If mixed venous oxygen saturation decreased to less than 65% despite appropriate arterial oxygenation (≥95%) and hemoglobin concentrations of 8 g/dL^{-1} or higher, arterial lactate concentrations increased, or both, we administered the nonadrenergic calcium sensitizer levosimendan to improve systemic oxygen delivery at a dose of 0.2 µg/kg/min (without a loading bolus dose) for 24 hours.

We recorded all hemodynamic measurements, laboratory variables, blood gas analyses, and norepinephrine requirements at baseline and at 24, 48, 72, and 96 hours after randomization. We also recorded adverse events, including death from any cause, occurring during the 28 days following randomization.

Sample Size Calculation

To detect a 20% change in heart rate (estimated standard deviation 40%) with a power of 80% and a type I error rate of .05, by using a 2-sided *t* test, we calculated that 64 patients per group would be required. Because data distribution was unknown a priori and data were analyzed by nonparametric analysis, we assumed a worst-case scenario with a minimal asymptotic relative efficiency of 0.864 for the Wilcoxon-Mann-Whitney test, resulting in a minimum required sample size of 75 patients per group.[13]

Statistical Analysis

We used SPSS version 20 (IBM Corp) for statistical analysis. Continuous data are summarized by median (interquartile range [IQR]), if not otherwise specified. We performed all analyses according to the intention-to-treat principle. We compared baseline and demographic data using the Wilcoxon-Mann-Whitney or χ^2 test, as appropriate. To avoid multiple comparisons, we calculated areas under the curve (AUCs) relative to baseline values for continuous variables with repeated measurements, as suggested by Matthews et al[14] (see eMethods in the Supplement for details). We then compared AUCs between the 2 treatment groups with the Wilcoxon-Mann-Whitney test. Binary 28-day mortality of the 2 groups was compared by a χ^2 test. In addition, we compared 28-day overall survival by means of a log-rank test and by fitting a multivariable Cox regression model. We built this latter model by using stepwise forward inclusion based on likelihood ratio *P* values for which study group assignment, sex, multidrug-resistant *Acinetobacter* or *Klebsiella* infection, and levosimendan infusion were considered as cofactors, and age, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), Simplified Acute Physiology Score (SAPS) II, baseline values of norepinephrine dosage, arterial lactate concentration, and platelet count were considered as covariables.[15,16] Survival plots for time-to-event outcomes were designed as recommended by Pocock et al.[17] We initially estimated mortality risk from the SAPS II score.[18] This is usually computed using the most extreme values collected over the first 24 hours following ICU admission, whereas we used values measured at study entry, by which time patient stabilization has usually generated a lower SAPS II score and thus underestimates mortality risk. Patients requiring high-dose norepinephrine, a requirement in our study, have a very high mortality.[19,20] The primary end point was confirmatory tested at a 2-sided significance level of α = .05. All other given *P* values are exploratory. Additional and alternative statistical approaches are detailed in the eMethods in the Supplement.

Results

Patients

After hemodynamic optimization, we screened 336 patients with 176 being excluded due to heart rate values of less than 95/min (n = 166) or previous β-blocker therapy (n = 10). In another 6 patients, we could not obtain informed consent. Thus, a total of 154 patients were included and randomly assigned to the 2 study groups in a 1:1 ratio (Figure 1).

Data on the primary end point were complete, whereas only 29 of 770 data sets (154 patients × 5 time points) had at least 1 laboratory variable missing (eg, troponin). To account for these missing data, calculation of AUC was based on the assumption that the missing value represents the mean of the values before and after.

Demographic Data

Baseline data were similar among study groups with respect to age, sex, BMI, comorbidities, SAPS II score, focus of sepsis,

Table 1. Baseline Characteristics of the Study Patients

	Esmolol (n = 77)	Control (n = 77)
Age, median (IQR), y	66 (52-75)	69 (58-78)
Men, No. (%)	54 (70)	53 (69)
Body mass index, median (IQR)[a]	29 (26-33)	28 (25-32)
SAPS II score, median (IQR)[b]	52 (47-60)	57 (49-62)
Norepinephrine dosage, median (IQR), μg/kg/min	0.38 (0.21-0.87)	0.40 (0.18-0.71)
Arterial lactate, median (IQR), mmol/L	1.5 (1.1-2.7)	1.9 (1.1-3.1)
Platelet count, median (IQR), × 10^3/μL	178 (126-272)	129 (73-206)
Fluid input, mL, 24 h prior to inclusion, median (IQR),	4700 (4300-5200)	4800 (4100-5325)
Cause of septic shock, No.		
Necrotizing fasciitis	1	2
Pyelonephritis	1	1
Peritonitis	21	30
Pneumonia	54	44
Pathogens, No. (%)		
Klebsiella spp	29 (38.0)	20 (26.0)
Acinetobacter spp	6 (7.8)	6 (7.8)
Acinetobacter spp + *Klebsiella* spp	11 (14.3)	8 (10.4)
Staphylococcus aureus	6 (7.8)	6 (7.8)
Escherichia coli	3 (3.9)	8 (10.4)
Pseudomonas spp	5 (6.5)	4 (5.2)
Aspergillus spp	0 (0.0)	3 (3.9)
Others	17 (22.0)	22 (28.6)
Preexisting conditions, No. (%)		
Coronary artery disease	25 (32.5)	21 (27.3)
Congestive heart failure	11 (14.3)	13 (16.9)
Chronic kidney disease	5 (6.5)	4 (5.2)
Chronic obstructive pulmonary disease	16 (20.8)	20 (26.0)

Abbreviation: IQR, interquartile range.

[a] Calculated as weight in kilograms divided by height in meters squared

[b] The Simplified Acute Physiology Score (SAPS) II is calculated from a point score of 12 routinely measured physiological and biochemical variables within the first 24 hours of intensive care unit admission. The range varies from 0 to 163 points with more extreme values scoring more points.[18]

pathogen spectrum, norepinephrine dose, and first 24-hour fluid input (**Table 1**). The high SAPS II score and the high norepinephrine requirement at study entry (Table 1) are indicative of patients who are at high risk of mortality.[17-19]

Study Drug Dosage

The median esmolol dosage was 100 mg/h (IQR, 50-300) without relevant trends over time (**Figure 2**). We did not exceed the maximum permitted dosage of 2000 mg/h.

Hemodynamic Variables and Other Therapies

The target range for heart rate was 80/min to 94/min in all patients in the esmolol group, which was significantly lower throughout the intervention period than what was achieved in the control group. The median AUC over the first 96 hours was −28/min (IQR, −37 to −21) for the esmolol group vs −6/min (−14 to 0) for the control group ($P < .001$; **Figure 3**). MAP was maintained despite a marked reduction in norepinephrine requirements in the esmolol group with a median AUC of −0.11 μg/kg/min (IQR, −0.46 to 0) vs −0.01 μg/kg/min (−0.2 to 0.44) in the control group ($P = .003$; Figure 3). Stroke volume, systemic vascular resistance, and left ventricular stroke work indices were increased in the esmolol group (Figure 3, **Table 2**). Although reductions in systemic oxygen delivery were greater in the esmolol group with a median AUC of −100 mL/min/m² (IQR, −211 to −38) vs −32 mL/min/m² (IQR, −108 to 21) in the control group ($P < .001$) and had reduced consumption with a median AUC of −29 mL/min/m² (IQR, −55 to 0) in the esmolol group vs −4 mL/min/m² (IQR, −29 to 20) in the control group ($P < .001$; eTable 1 in the Supplement), the need for levosimendan rescue therapy did not differ between groups (49.4% of esmolol patients vs 40.3% control patients; $P = .39$). Fluid requirements were reduced in the esmolol group with a median AUC of 3975 mL/24 h (IQR, 3663 to 4200) vs 4425 mL/24 h (IQR, 4038 to 4775) in the control group ($P < .001$; Table 2). We could find no clinically relevant difference between treatment groups for any other systemic or pulmonary hemodynamic variable.

Acid-Base and Metabolic Variables

The median AUCs were higher for arterial pH for the esmolol group: 0.28 units (IQR, −0.01 to 0.08) vs −0.02 units (IQR, −0.06 to 0.06) for the control group ($P = .003$) and for base excess, 0.8 mmol/L (−1.2 to 3.6) for the esmolol group vs −0.5 mmol/L (IQR, −2.1 to 2.8) for the control group ($P = .03$), whereas the median AUC for arterial lactate concentration was lower for the esmolol group at −0.1 mmol/L (IQR −0.6 to 0.3) than for the control group at 0.1 mmol/L (IQR, −0.3 to 0.6; $P = .006$). Partial gas pressures and oxygen saturations did not differ between groups (eTable 1 in the Supplement).

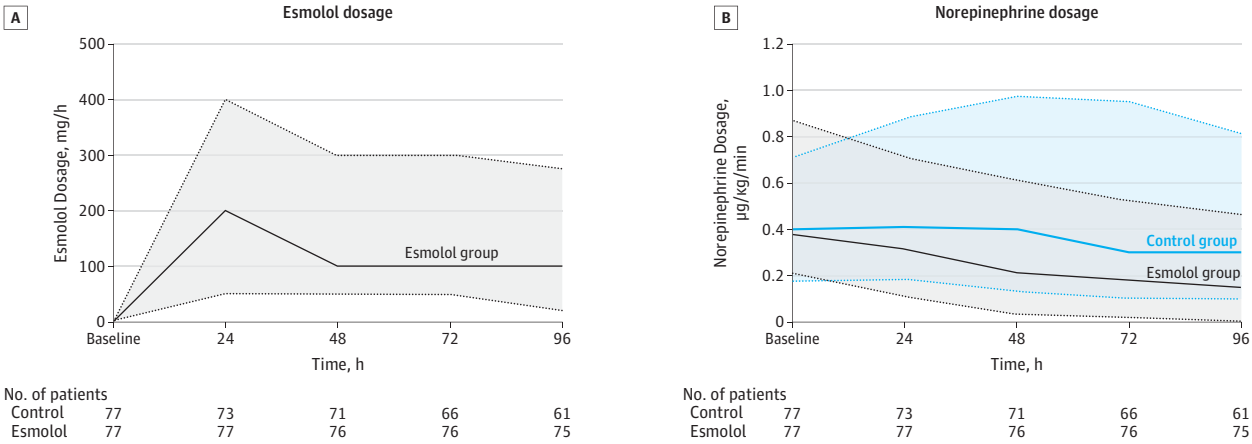
Markers of Organ Function and Injury

Kidney function, assessed by the Modification of Diet in Renal Disease formula for estimating glomerular filtration rate, was better maintained in the esmolol group: median AUC of 14 mL/min/1.73 m² (IQR, 4 to 37) than in the control group vs 2 mL/min/1.73 m² (IQR, −7 to 20; $P < .001$). The trend remained when excluding patients receiving renal replacement therapy with a median AUC in the esmolol group of 10 mL/min/1.73 m² (IQR, 1 to 35) vs −2 mL/min/1.73 m² (IQR, −9 to 4) in the control group ($P < .001$; **Figure 4**). During ICU stay, the percentage of patients requiring renal replacement therapy did not differ between groups: 40.3% in the esmolol group vs 41.6% in the control group. The arterial oxygen partial pressure to inspired oxygen fraction ratio was higher in the esmolol group with a median AUC of 38 mm Hg (IQR, −22 to 72) than in the control group 6 mm Hg (IQR, −46 to 59; $P = .03$). Liver function tests did not differ between groups, whereas markers of myocardial injury were lower in the esmolol group with the median AUC for troponin T in the esmolol group being −0.01 (IQR, −0.05 to 0.00) vs 0.00 (IQR, −0.01 to 0.02) for the control group ($P = .002$) and the CK-MB for the esmolol group was −1 (IQR, −4 to 0) vs control 0 (IQR, −1 to 1) for the control group ($P = .02$; eTable 2 in the Supplement).

Outcome Data

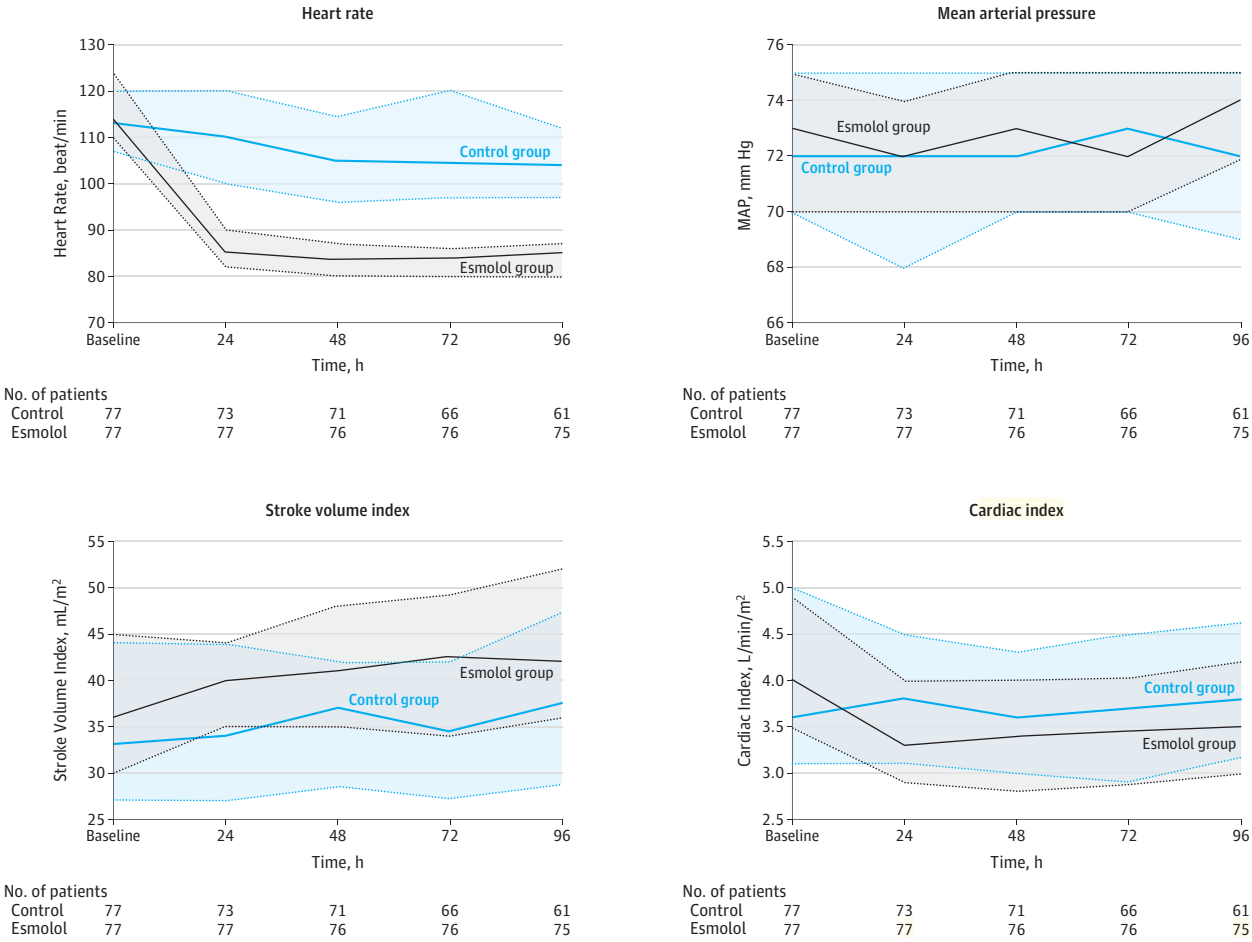
The esmolol group had a 28-day mortality rate of 49.4% vs 80.5% in the control group ($P < .001$). Overall survival was higher in the esmolol group (**Figure 5**). Multivariable Cox regression analysis revealed that esmolol group allocation (hazard ratio [HR], 0.392; 95% CI, 0.261-0.590; $P < .001$) and SAPS

Figure 2. Esmolol and Norepinephrine Drug Infusions in Study Patients



Solid lines represent median values. The shaded areas bordered by dotted lines represent the upper and lower quartiles by colors.

Figure 3. Changes in Hemodynamic Variables



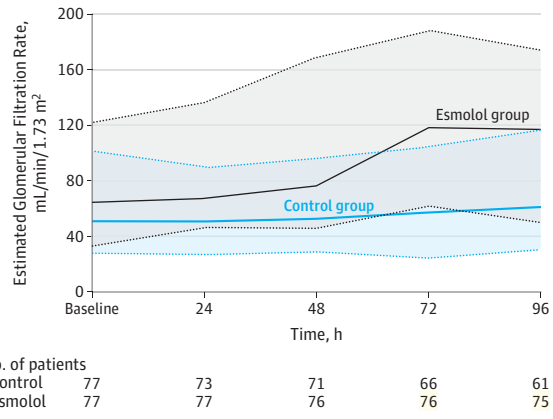
Solid lines represent median values. The shaded areas bordered by dotted lines represent the upper and lower quartiles. MAP indicates mean arterial pressure.

Table 2. Hemodynamic Variables of Study Patients

Group	Median (Interquartile Range)						*P* Value, Wilcoxon-Mann-Whitney
	Baseline	24 Hours	48 Hours	72 Hours	96 Hours	Area Under the Curve	
Pressure, mm Hg							
RAP							
Esmolol	12 (10 to 15)	14 (11 to 16)	14 (11 to 15)	13 (10 to 15)	13 (11 to 15)	1 (−1 to 3)	.17
Control	13 (9 to 15)	12 (10 to 15)	12 (10 to 15)	13 (9 to 15)	12 (9 to 15)	0 (−2 to 2)	
PAWP							
Esmolol	17 (14 to 20)	17 (15 to 20)	17 (15 to 19)	17 (14 to 19)	16 (14 to 18)	0 (−2 to 2)	.48
Control	17 (14 to 20)	17 (14 to 20)	17 (15 to 19)	17 (14 to 19)	17 (14 to 19)	0 (−2 to 1)	
MPAP							
Esmolol	31 (28 to 34)	30 (27 to 33)	29 (27 to 32)	30 (26 to 32)	29 (25 to 32)	−1 (−1 to 0)	.34
Control	31 (27 to 34)	29 (27 to 34)	30 (27 to 32)	30 (25 to 33)	28 (25 to 33)	−1 (−2 to 1)	
Resistance pressure, dyn.s/cm^5/m^2							
SVRI							
Esmolol	1148 (970 to 1362)	1382 (1171 to 1653)	1370 (1149 to 1668)	1403 (1141 to 1708)	1411 (1137 to 1616)	264 (33 to 439)	<.001
Control	1271 (967 to 1548)	1265 (1031 to 1608)	1326 (1086 to 1614)	1359 (1026 to 1678)	1276 (985 to 1586)	90 (−74 to 231)	
PVRI							
Esmolol	253 (188 to 309)	293 (206 to 393)	270 (195 to 415)	281 (198 to 385)	286 (197 to 360)	38 (−12; 84)	.02
Control	282 (214 to 347)	289 (197 to 389)	286 (231 to 348)	286 (216 to 384)	261 (221 to 326)	8 (−24 to 40)	
Stroke work index, mL/m^2							
Left ventricle							
Esmolol	27 (23 to 33)	31 (24 to 34)	32 (26 to 37)	32 (25 to 39)	34 (28 to 41)	3 (−1 to 8)	.03
Control	24 (19 to 31)	26 (19 to 31)	28 (21 to 34)	27 (21 to 32)	31 (23 to 36)	1 (−3 to 5)	
Right ventricle							
Esmolol	9 (6 to 12)	9 (7 to 12)	9 (7 to 11)	9 (7 to 12)	9 (7 to 12)	0 (−2 to 2)	.69
Control	8 (6 to 10)	9 (7 to 10)	8 (7 to 12)	8 (6 to 11)	8 (7 to 11)	0 (−1 to 1)	
Fluid infusion, mL/24 h							
Esmolol		5000 (4300 to 5400)	4600 (4300 to 5000)	4300 (4000 to 4600)	4000 (3600 to 4300)	3975 (3663 to 4200)	<.001
Control		5200 (4700 to 5800)	5400 (4900 to 5700)	5200 (4800 to 5600)	5400 (4725 to 6000)	4425 (4038 to 4775)	

Abbreviations: MPAP, mean pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; PVRI, pulmonary vascular resistance index; RAP, right atrial pressure; RVSWI, right ventricular stroke work index; SVRI, systemic vascular resistance index.

Figure 4. Estimated Glomerular Filtration Rate Using the Modification of Diet in Renal Disease Formula



Black lines represent median values for the esmolol group; blue, the control group. The shaded areas represent the upper and lower quartiles. Patients receiving renal replacement therapy were excluded from analysis.

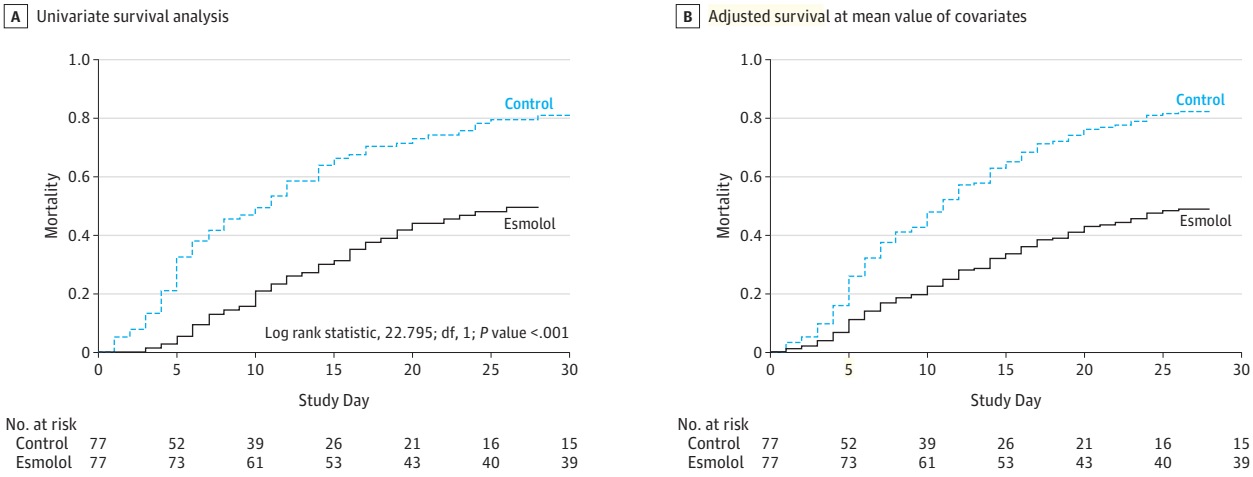
II score (HR, 1.033; 1.013-1.054; $P < .001$) were the only variables to be included in the model for optimal prediction of overall survival (eAppendix in the Supplement). However, the esmolol dose did not influence 28-day mortality (odds ratio [OR], 1.000; 95% CI, 0.999-1.001; **Table 3**)

Discussion

In a cohort of patients with septic shock and high risk of mortality, our open-label use of esmolol after initial hemodynamic optimization resulted in maintenance of heart rate within the target range of 80/min to 94/min. Compared with standard treatment, esmolol also increased stroke volume, maintained MAP, and reduced norepinephrine requirements without increasing the need of inotropic support or causing adverse effects on organ function. There was an associated improvement in 28-day survival.

Tachycardia increases cardiac workload and myocardial oxygen consumption. In addition, shortening of diastolic relaxation time and impairment of diastolic function further

Figure 5. Survival Analysis of Study Patients



A, unadjusted survival plots (Kaplan-Meier) of patients. B, multivariable adjusted survival (Cox) at mean values of Simplified Acute Physiology Score II. Ordinate axis is scaled as "1-survival" to depict the 0 intersection without breaking the axis.

Table 3. Outcome Data of Study Patients

Outcome	No. (%) Esmolol (n = 77)	No. (%) Control (n = 77)	*P* Value
Mortality			
28 d	38 (49.4)	62 (80.5)	<.001
ICU	44 (57.1)	68 (88.3)	<.001
Hospital	52 (67.5)	70 (90.9)	<.001
Length of ICU stay, d			
Median (IQR)	19 (11-27)	14 (7-25)	.03
Survivors', median (IQR)	17 (9-28)	21 (11-34)	.70
Cause of death, No./total, (%)			
Multiple organ failure	15/52 (28.8)	26/70 (37.1)	.71
Refractory hypotension	32/52 (61.6)	44/70 (62.9)	
Unknown cause	5/52 (9.6%)		

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

affect coronary perfusion, contributing to a lower ischemic threshold.[21] Excessive sympathetic activation also leads to catecholamine-induced cardiomyocyte toxic effects characterized by inflammation, oxidative stress, and abnormal calcium handling resulting in left ventricular dilatation, apical ballooning, myocardial stunning, apoptosis, and necrosis.[9,22,23] Taken together, these mechanisms contribute to worsening of septic myocardial dysfunction and increased mortality.[6-8]

Treating tachycardia in septic shock is controversial. The right timeframe for intervention and the optimal heart rate threshold are currently undefined. In the early unresuscitated phase of septic shock, tachycardia represents the main mechanism to compensate for any decrease in cardiac output.[21] In this case, heart rate reduction may derail this adaptive physiologic response, leading to a decrease in oxygen delivery that may compromise organ perfusion and function. Adequate volume resuscitation will often result in a concomitant decrease in heart rate yet, in some septic patients, tachycardia persists despite excluding other causes such as pain and agitation. Tachycardia may in such cases represent an expression of sympathetic overstimulation, in part due to activation of peripheral afferent fibers by ischemia and inflammation in peripheral tissues.[21,24]

Although reducing heart rate will decrease myocardial oxygen consumption and will improve diastolic function and coronary perfusion, for patients with sepsis, an inadequate chronotropic response may potentially negatively affect cardiac output and tissue perfusion. Predefining a threshold value for heart rate is difficult because it must be individualized in the context of the patient's overall hemodynamic status and any preexisting comorbidities.[21] In our study, we hypothesized that a heart rate range between 80/min to 94/min was a sufficient compromise between improving cardiac performance and preserving systemic hemodynamics. We found no obvious safety issues related to the use of esmolol, a finding reflected in an open-label study of oral metoprolol given to patients with septic shock who had myocardial depression for which heart rate control (targeted at 65/min-95/min) was successfully achieved

in 97.5% of patients within a mean 12 (SD, 12) hours.[12] Esmolol has the advantage of being ultrashort-acting with a half-life of approximately 2 minutes.[25] This simplifies titration against a predefined heart rate target and enables rapid resolution of any potential adverse effect after drug discontinuation. Targeted heart rates between 80/min to 94/min were achieved safely within the first 24 hours of treatment. Importantly, the norepinephrine-sparing effect was not associated with a higher need for inotropic support but rather by an increase in left ventricular stroke work. These findings suggest that lowering of heart rate by esmolol allows better ventricular filling during diastole, hence, improving stroke volume and thereby improving the efficiency of myocardial work and oxygen consumption. Together with an amelioration in catecholamine-induced toxicity, myocardial performance may be preserved during septic shock thereby facilitating survival. Administration of esmolol improved markers of tissue perfusion and organ injury, with no obvious compromise of organ function.

Adverse effects of catecholamines may become manifest over the whole course of a patient's illness, affecting organs other than the heart. Examples include lung (pulmonary edema, pulmonary hypertension), gastrointestinal tract (inhibition of peristalsis, bowel ischemia), coagulation system (hypercoagulability, thrombus formation), immune system (immunomodulation, stimulation of bacterial growth), metabolism (increases in cellular energy expenditure, hyperglycemia and impaired glucose tolerance, muscle catabolism, increased lipolysis, and hyperlactatemia).[5,6,26] Because noncardiac actions of β-blocker therapy may also prove beneficial, we chose to continue esmolol therapy with maintenance of the heart rate target range throughout the patient's ICU stay.

Study limitations include selection of an arbitrary predefined heart rate threshold rather than an individualized approach titrated to specific myocardial characteristics or other biomarkers. We adopted a heart rate threshold of less than 95/min because values persisting above this level are associated with adverse cardiac events in ICU patients.[7] Second, the study had to be nonblinded because titration of esmolol to achieve heart rate control was the primary objective. Inactive placebo would be ineffective in lowering heart rate (unless covert hypovolemia was present) and large volumes of fluid attempting to achieve this goal may prove deleterious. Third, enrollment was performed in an environment of high-endemic rates of multidrug-resistant *Klebsiella* and *Acinetobacter baumannii* strains that may have led to secondary complications. Multivariable analysis was performed to account for this infectious burden and other potential confounders. Fourth, we cannot conclude to what extent noncardiac mechanisms of esmolol contributed to the observed improvement in mortality nor conclude whether it was simply the reduction in heart rate alone. An ongoing study of heart rate control in critically ill patients using the funny channel current inhibitor, ivabradine will help to address this point.[27]

Fifth, although mortality was not a primary end point, the unexpectedly large intergroup difference does not exclude the possibility of a chance finding or a contribution from unknown confounding factors. We did investigate a population in severe septic shock with sustained tachycardia and requiring high-dose norepinephrine, all of which are indicative of a very poor prognosis.[6-8,19,20] This high-risk subset would likely gain the greatest benefit from heart rate control by β-blockade. Whether similar benefits are achieved in less sick patients requires further investigation. Appropriately powered, randomized, controlled multicenter trials are required to confirm our findings.

Conclusion

For patients in septic shock, the open-label use of esmolol was able to achieve reductions in heart rate to target levels, without an increase in adverse outcomes compared with standard treatment. Further investigation of the effects of esmolol on clinical outcomes is warranted.

ARTICLE INFORMATION

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