Arterial Blood Pressure and Neurologic Outcome After Resuscitation From Cardiac Arrest*

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**Objectives:** Guidelines for post–cardiac arrest care recommend blood pressure optimization as one component of neuroprotection. Although some retrospective clinical studies suggest that postresuscitation hypotension may be harmful, and laboratory studies suggest that a postresuscitation hypertensive surge may be protective, empirical data are few. In this study, we prospectively measured blood pressure over time during the postresuscitation period and tested its association with neurologic outcome.

**Design:** Single center, prospective observational study from 2009 to 2012.

**Patients:** Inclusion criteria were age 18 years old or older, pre-arrest independent functional status, resuscitation from cardiac arrest, and comatose immediately after resuscitation.

**Measurements and Main Results:** Our research protocol measured blood pressure noninvasively every 15 minutes for the first 6 hours after resuscitation. We calculated the 0- to 6-hour time-weighted average mean arterial pressure and used multivariable logistic regression to test the association between increasing time-weighted average mean arterial pressures and good neurologic outcome, defined as Cerebral Performance Category 1 or 2 at hospital discharge. Among 151 patients, 44 (29%) experienced good neurologic outcome. The association between blood pressure and outcome appears to have a threshold effect at time-weighted average mean arterial pressure value of 70 mm Hg. This threshold (mean arterial pressure > 70 mm Hg) had the strongest association with good neurologic outcome (odds ratio, 4.11; 95% CI, 1.34–12.66; p = 0.014). A sustained intrinsic hypertensive surge was relatively uncommon and was not associated with neurologic outcome.

**Conclusions:** We found that time-weighted average mean arterial pressure was associated with good neurologic outcome at a threshold of mean arterial pressure greater than 70 mm Hg. (Crit Care Med 2014; 42:2083–2091)

**Key Words:** brain injury; cardiopulmonary resuscitation; ischemia-reperfusion injury; return of spontaneous circulation

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*See also p. 2145.

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The post–cardiac arrest syndrome is a state of severe, global ischemia/reperfusion injury with potentially devastating consequences (1, 2). The mortality associated with this condition is extremely high, and among those that survive, many are left with permanent, disabling neurologic injury. The discovery that controlling body temperature after return of spontaneous circulation (ROSC) may improve neurologic function (3–5) provides hope that additional postresuscitation interventions may be found to reduce the degree of brain injury and further improve clinical outcomes.

Patients with post–cardiac arrest syndrome experience ongoing oxidant damage (6, 7), profound systemic inflammation (8–10), myocardial stunning (11, 12), and adrenal axis suppression (13, 14), which commonly result in major hemodynamic instability (15–18). Given that the injured brain commonly has dysfunctional autoregulation of the cerebral blood flow, including brain injury secondary to cardiac arrest (19, 20), it is possible that post-ROSC blood pressure alterations may be a factor in ongoing cerebral injury and eventual neurologic outcome. With disruption of normal cerebrovascular autoregulation, cerebral blood flow may become directly related to cerebral perfusion pressure (20), which is dependent on mean arterial pressure (MAP).

Although some retrospective clinical studies suggest that postresuscitation hypotension is associated with lower survival (16–18, 21), and laboratory studies suggest that inducing a postresuscitation hypertensive surge may confer
neuroprotection (22, 23), there remains a paucity of data on the relationship between post-ROSC blood pressure and neurologic outcome. The 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care recommend post-ROSC goal-directed hemodynamic support including blood pressure optimization with IV fluids and vasopressors to achieve a target MAP greater than or equal to 65 mm Hg (24). However, the relationship between post-ROSC MAP and neurologic outcome remains incompletely understood. Specifically, it is unclear if there is an association between MAP and neurologic outcome, and if they are associated, it is unknown if it is a threshold effect at a specific low MAP value versus a linear relationship in which hypertension is protective.

In this prospective observational study of adult patients resuscitated from cardiac arrest, our objectives were to measure blood pressure over time in the immediate postresuscitation period and to test the association between postresuscitation blood pressure and neurologic outcome at hospital discharge. We hypothesized that higher post-ROSC blood pressures would be independently associated with good neurologic outcome.

**METHODS**

**Setting**

This was a prospective observational study conducted at a single urban academic medical center, Cooper University Hospital in Camden, New Jersey. Subjects were enrolled in the emergency department (ED) and ICU from 2009 to 2012. The institutional review board approved this study with a waiver of written informed consent.

**Participants**

We enrolled in- and out-of-hospital adult post–cardiac arrest patients who were comatose immediately after ROSC. The inclusion criteria were 1) age 18 years old or older; 2) independent functional status prior to cardiac arrest; 3) cardiac arrest, defined as a documented absence of pulse and CPR initiated; 4) ROSC; and 5) inability to follow commands immediately after ROSC. We excluded patients with cardiac arrest related to trauma. We also excluded patients if, for any reason, post-ROSC blood pressure recordings were not captured per protocol (see detail described below). Figure 1 displays our screening process.

**Patient Identification**

We used the following methodology previously described for real-time, prospective identification of post–cardiac arrest patients (25). This included a 24-hour per day, 7-day per week paging system activated in one of two ways: 1) a hospital-wide “code blue” activation anytime a cardiac arrest occurred in the hospital; 2) ED unit secretaries were trained to activate a page when an out-of-hospital cardiac arrest arrived in the ED (or a cardiac arrest occurred in the ED). An investigator received the page and responded to the cardiac arrest event to begin data capture.

**Post–Cardiac Arrest Care**

Our institution uses state-of-the-art postresuscitation care for post–cardiac arrest patients and a previously published standard operating procedure, by our group, including all of the following elements recommended for regional cardiac arrest centers: 1) immediate evaluation for percutaneous coronary intervention (if needed); 2) immediate evaluation for therapeutic hypothermia; 3) evaluation and management by an in-house critical care physician; and 4) evidence-based timing and methods of neurologic prognostication (26, 27). Our institution uses a standardized order set for treatment with therapeutic hypothermia, using a surface cooling system (Arctic Sun, Medivance, Louisville, CO), and our clinicians have demonstrated proficiency in achieving and maintaining target temperature (33–34°C) in 96% of cases, within a median time of 4.4 hours from ROSC (28). The decision on whether or not to initiate therapeutic hypothermia was made by the treating physicians and was not part of the study protocol. In general, our clinicians use therapeutic hypothermia for out-of-hospital cardiac arrest due to ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT) (i.e., level 1 recommendation in the current guidelines) (24), and its use in other patients (e.g., nonshockable initial rhythm or in-hospital cardiac arrest) is at the discretion of the treating physician.

**Data Collection**

We collected basic demographics as well as the data and outcome variables consistent with the Utstein style for reporting cardiac arrest research, including the post-ROSC variables recommended for postresuscitation research (29, 30). For measuring the exposure of interest (arterial blood pressure over time), our research protocol cycled a noninvasive blood pressure cuff every 15 minutes for the first 6 hours after ROSC and recorded all blood pressure measurements. We entered the data into a dedicated Access database (Microsoft Corporation, Redmond, WA) and exported to StatPlus:mac version 2009 (AnalystSoft, Alexandria, VA) for analysis.

**Outcome Measures**

The primary outcome was good neurologic function at hospital discharge, defined as a Cerebral Performance Category
(CPC) 1 or 2, which is the most commonly used outcome measure in clinical trials of post–cardiac arrest interventions (31). The CPC is a validated five-point scale of neurologic disability (1: good cerebral performance, 2: moderate cerebral disability, 3: severe cerebral disability, 4: coma/vegetative state, and 5: death) (29, 32, 33). Patients with a CPC of 1 or 2 had sufficient cerebral function at discharge to live independently.

**Data Analysis**

We began our analysis with descriptive statistics. We described continuous data as mean values and so or median values and interquartile range (IQR), based on distribution of data, and displayed categorical data as counts and proportions.

**Quantifying the Exposure.** For each post–cardiac arrest patient, we calculated the time-weighted average mean arterial pressure (TWA-MAP) for the first 6 hours after ROSC. We calculated the TWA-MAP for each patient in a manner consistent with previously published methods of calculating exposures over time in epidemiological research (34–36). For each patient, we multiplied the length of time that the patient spent at a specific MAP value by that MAP value, added all these values together, and then divided by the total length of postresuscitation observation time. Thus, we used the equation:

\[
\text{TWA-MAP} = \frac{\left[(\text{MAP}_a \times \text{Time}_a) + (\text{MAP}_b \times \text{Time}_b) + \ldots (\text{MAP}_z \times \text{Time}_z)\right]}{(\text{Time}_a + \text{Time}_b + \ldots \text{Time}_z)}
\]

For example, if a patient had the following exposures—MAP 70 mm Hg for 30 minutes, MAP 72 mm Hg for 15 minutes, MAP 74 mm Hg for 60 minutes, MAP 77 mm Hg for 45 minutes, MAP 80 mm Hg for 60 minutes, MAP 82 mm Hg for 45 minutes, MAP 85 mm Hg for 60 minutes, and MAP 87 mm Hg for 45 minutes, the TWA-MAP for the 6-hour postresuscitation period would be: \((2,100 \text{ mm Hg} \times \text{min} + 1,080 \text{ mm Hg} \times \text{min} + 5,440 \text{ mm Hg} \times \text{min} + 3,465 \text{ mm Hg} \times \text{min} + 4,800 \text{ mm Hg} \times \text{min} + 3,690 \text{ mm Hg} \times \text{min} + 5,100 \text{ mm Hg} \times \text{min} + 3,915 \text{ mm Hg} \times \text{min})/360 \text{ min} = 79 \text{ mm Hg} \). Thus, this value, 79 mm Hg, would be the time-weighted average value for the MAP over the duration of the 6-hour period.

We calculated odds ratios (ORs) using multivariate logistic regression to determine if the TWA-MAP was independently associated with neurologic function at hospital discharge. To test if the TWA-MAP had a linear association with neurologic outcome, we entered TWA-MAP into the model as a continuous variable. To test if the association was a threshold effect at a specific arterial blood pressure, we performed additional multivariate logistic regression analyses, each with TWA-MAP at different binary cutoffs (5 mm Hg increments from MAP > 65 mm Hg to MAP > 90 mm Hg). We selected the following candidate variables for the regression models on the grounds that they were previously demonstrated to predict outcome in post–cardiac arrest patients: 1) age (decile), 2) initial cardiac rhythm (i.e., VF/VT vs asystole or pulseless electrical activity [PEA]), and 3) prearrest comorbidities (i.e., Charlson comorbidities index) (24, 37–39).

**Sample Size Calculation.** To ensure adequate power to test these four covariates in a multivariate model, we estimated the necessary sample size, based on the following assumptions: 1) a predicted survival with good neurologic function rate of 28% (40); and 2) an estimated event (survival with good neurologic function) per covariate ratio of 10:1 necessary for multivariate modeling (41, 42). In order to accrue the necessary 40 survivors with good neurologic function, we estimated that a minimum of 143 total subjects would be necessary.

**RESULTS**

One hundred fifty-one patients met all inclusion and no exclusion criteria and were enrolled. Table 1 displays baseline characteristics. The mean (sd) age of subjects was 63 (± 16) years. Sixty-four (42%) were women. The majority of the subjects in the cohort had an in-hospital arrest, and most had an initial recorded rhythm of PEA or asystole. Eighty-six of the subjects (57%) required a continuous infusion of vasopressor agents in the first 6 hours after ROSC.

Therapeutic hypothermia was used in 16 of 23 patients (70%) with out-of-hospital arrest, and 52 of 151 of all patients (34%). In the treated population, target temperature was achieved in 46 of 52 patients (88%), with a median (IQR) time to target temperature of 3.9 hours (2.8–4.9 hr). Good neurologic outcome occurred in 26% of those treated versus 31% of patients not treated with therapeutic hypothermia (\(p = 0.578\), using Fisher exact test). The majority of those treated with therapeutic hypothermia (42 of 54 [78%]) had PEA/asystole as initial rhythm.

The mean (sd) TWA-MAP for the entire cohort was 79 (± 17). Figure 2 displays the distribution of TWA-MAP values and shows that sustained low arterial pressure, for example, TWA-MAP less than or equal to 70 mm Hg, was relatively common (25% of patients), whereas an intrinsic sustained hypertensive surge, for example, TWA-MAP greater than 100 mm Hg, was relatively uncommon (< 10% of patients).

Twenty-nine percent (44 of 151) of all patients were found to have the primary outcome of good neurologic function at hospital discharge. Fourteen (32%) of those who met the primary outcome had initial rhythm of VF/VT. Twenty-nine percent (14 of 49) of those with an initial rhythm of VT/VF had a good neurologic outcome and likewise 29% (30 of 102) of those with an initial rhythm of PEA/asystole had a good neurologic outcome.

The mean (sd) TWA-MAP among patients with good neurologic function and poor neurologic function at hospital discharge was 83 (± 13) and 77 (± 18), respectively (\(p = 0.042\). Figure 3 displays the good neurologic function at hospital discharge in relation to the TWA-MAP value for the first 6 hours after ROSC.

Table 2 displays the results of the multivariate logistic regression model with TWA-MAP as a continuous independent variable and good neurologic function at hospital discharge as the
dependent variable (OR, 1.02; 95% CI, 1.00–1.02; \( p = 0.086 \)). Table 3 displays additional multivariate logistic regression models with TWA-MAP at different binary thresholds. There appears to be a threshold effect at a TWA-MAP greater than 70 mm Hg. We found that a TWA-MAP greater than 70 mm Hg was the highest blood pressure threshold that was independently associated with the outcome. That is, in starting at a MAP of 90 mm Hg and decreasing the binary cutoff by 5 mm Hg increments, TWA-MAP first becomes an independent predictor of outcome at a threshold greater than 70 mm Hg. A TWA-MAP greater than 70 mm Hg also had the highest OR for good neurologic function at hospital discharge among all binary thresholds tested, OR 4.11 (95% CI, 1.34–12.66, \( p = 0.014 \)). On further sensitivity analysis, TWA-MAP greater than 70 mm Hg remained the MAP threshold with the strongest association with good neurologic outcome after adjusting for duration of CPR or “downtime” longer than 10 minutes, OR 5.25 (95% CI, 1.73–15.98, \( p = 0.003 \)) (details of the models are displayed in the supplemental data, Supplemental Digital Content 1, http://links.lww.com/CCM/A971). Table 4 reports neurologic outcome as it relates to vasopressor use in the first 6 hours after ROSC.

**DISCUSSION**

In this prospective observational study, we tested the relationship between arterial blood pressure after resuscitation from cardiac arrest and neurologic outcome. We sought to test this relationship because the injured brain may be especially vulnerable to blood pressure alterations after ROSC due to a loss of normal cerebral autoregulation and disruption of microvascular perfusion (19, 20), and thus maintaining an adequate MAP (or raising the MAP) in the postresuscitation period may help ensure adequate cerebral perfusion and confer neuroprotection. To date, there has been little empirical data on this topic in human subjects, limited only to retrospective analyses (16–18) and one recent pilot study (43); thus, we felt that a rigorous prospective study with dense data capture of blood...
pressure recordings over time in the immediate postresuscitation period was needed.

We found that of the 151 patients enrolled, 29% (44 of 151) met our primary outcome of good neurologic outcome at hospital discharge; this is consistent with the outcomes in previously published large series of patients successfully resuscitated from cardiac arrest (40). We found that arterial hypotension was common while relatively fewer patients had an intrinsic hypertensive surge. On multivariate logistic regression analyses, we found that TWA-MAP was associated with good neurologic outcome. This association appears to be driven by the strong association between hypotension and poor neurologic outcome, as opposed to an association between intrinsic hypertension and better neurologic outcome. In our analysis, there was a threshold effect with a TWA-MAP greater than 70 mm Hg having the greatest association with good neurologic function, and we did not find higher MAP thresholds (> 75, > 80, > 85 mm Hg, etc.) to be associated with favorable neurologic outcome.

In contrast to some prior studies, a major strength of the current study is the prospective, dense data capture of blood pressure recordings over the early postresuscitation period to allow rigorous measurement of the true “exposure” and using TWA as mechanism of quantifying the exposure; the uniqueness of the results is that they provide more granular data on the relationship between blood pressure and neurologic outcome by identifying a numeric threshold of potential harm. In 2008, the International Liaison Committee on Resuscitation identified that determining the optimal target range for MAP after cardiac arrest was a critical knowledge gap in post–cardiac arrest care (2). This is an important area of clinical investigation, as sudden cardiac arrest is a leading cause of death and neurologic devastation among adults (44–46). Furthermore, the post–cardiac arrest syndrome is typically characterized with marked swings in blood pressure due to fluctuating hemodynamic perturbations after reperfusion (2, 15–18). Therefore, this
study addresses a clinical scenario that is relatively common and represents a critical phase in the trajectory of the eventual outcome following cardiac arrest.

The 2010 American Heart Association guidelines for post–cardiac arrest care recommended post-ROSC goal-directed hemodynamic optimization; however, the guidelines acknowledged the lack of high-quality evidence to support a specific target for MAP after ROSC (24). As there is proven benefit of goal-directed hemodynamic optimization, including MAP targets, for patients with other etiologies of critical illness (47–49), it is also, in theory, possible that blood pressure optimization could improve neurologic outcome among patients with post–cardiac arrest syndrome. However, this hypothesis has not yet been tested in a clinical trial. In a subanalysis of our study population, we found that patients who were able to maintain a TWA-MAP greater than 70 mm Hg without vasopressor administration had a higher proportion of good neurologic outcome compared with patients who achieved a TWA-MAP greater than 70 with vasopressor administration, 48% versus 24%, respectively (p = 0.01). We were unable to show a statistically significant difference in good neurologic outcome for patients administered vasopressors to maintain TWA-MAP greater than 70 mm Hg compared with patients with a TWAMAP less than or equal to 70 who did not receive vasopressors, 24% versus 10%, respectively (Table 4). One possibility to explain these findings is that the body’s intrinsic ability to maintain adequate perfusion pressure without vasopressors after ROSC is a predictor of eventual good neurologic outcome and that supporting the MAP with the application of vasopressor agents may not confer benefit. However, animal models have shown evidence to the contrary, in fact reporting that an induced hypertensive surge for cerebral blood flow promotion can attenuate brain injury and improve outcome (22, 23, 50, 51). Our study design did not test a vasopressor therapeutic approach, and we found fewer patients with sustained intrinsic hypertension than expected (12 of 151 had TWA-MAP > 100 mm Hg) with no clear association between TWA-MAPs greater than 90 mm Hg and good outcome, OR 1.12 (95% CI, 0.48–2.60, p = 0.794). We found only one clinical study that tested this induced hypertensive surge hypothesis, a recently published pilot interventional trial of induced hypertension after cardiac arrest, which reported that supranormal MAP did not affect cerebral tissue oxygenation (43).

Regarding blood pressure support after cardiac arrest and outcome, there may be important parallels between the global cerebral ischemia/reperfusion injury of cardiac arrest and the regional ischemia/reperfusion injury of acute ischemic stroke (AIS). In patients with AIS, it is widely accepted that arterial hypotension is associated with worse outcomes because it exacerbates cerebral ischemia, and permissive hypertension could preserve cerebral perfusion in the ischemic penumbra and protect the injured brain from further insult (52–63). Although ideal target blood pressure after cardiac arrest remains unknown, enough evidence exists to compel clinicians at the bedside pay close attention to blood pressure, specifically avoiding hypotension after resuscitation from cardiac arrest.

Limitations

We acknowledge that our data have important limitations to consider. Most notably, this was an observational study. Although many patients in the study received vasoactive agents, this was not an interventional protocol with a predefined MAP goal. Thus, we can only report associations in this study rather than infer causation.

By study design, we did not require invasive blood pressure monitoring nor could we control for the effects on outcome created by having various clinicians involved in patient care. Our study does, however, reflect real clinical practice and a readily available marker of inadequate perfusion (cuff blood pressure). Although our institution used a standardized order set for therapeutic hypothermia (28), and our clinicians have previously demonstrated a median time to achieving target temperature that was less than 4 hours (compared with 8 hr in the Hypothermia After Cardiac Arrest trial) (5), there was likely some degree of heterogeneity in the selection of patients for therapeutic hypothermia. As expected, the majority of cardiac arrest cases were in-hospital, nonshockable initial rhythms—a population where the efficacy of hypothermia is not clearly established (class IIb evidence)—and thus the practice at our hospital was driven by institutional policy rather than by randomized trial evidence.

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### Table 2. Multivariate Logistic Regression Model of the Association Between Time-Weighted Average Mean Arterial Pressure During the First 6 Hours After Return of Spontaneous Circulation and Good Neurologic Outcome (Defined as Cerebral Performance Category 1 or 2) at Hospital Discharge

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% Lower CI</th>
<th>95% Upper CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure</td>
<td>1.02</td>
<td>1.00</td>
<td>1.04</td>
<td>0.086</td>
</tr>
<tr>
<td>Age</td>
<td>0.93</td>
<td>0.75</td>
<td>1.15</td>
<td>0.490</td>
</tr>
<tr>
<td>Pulseless electrical activity/asystole initial rhythm</td>
<td>0.45</td>
<td>0.20</td>
<td>1.05</td>
<td>0.064</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>0.88</td>
<td>0.62</td>
<td>1.25</td>
<td>0.474</td>
</tr>
</tbody>
</table>

OR = odds ratio.

Time-weighted average mean arterial pressure is entered into the model as a continuous variable.
This study was limited to a single medical center, and thus, the sample size led to the wide CIs for the adjusted ORs on the multivariable logistic regression model (Table 3). Although the CIs are wide for the threshold cutoff of MAP greater than 70 mm Hg for a good neurologic outcome (OR, 4.11; 95% CI, 1.34–12.66), they remain significant (p = 0.014).

Lastly, although we used multivariable logistic regression analyses to adjust for cardiac arrest characteristics known to predict poor outcomes, there always exists the potential of unmeasured confounders with an observational design.

There appears to be a threshold effect at a TWA-MAP > 70 mm Hg. A TWA-MAP > 70 mm Hg is the highest blood pressure value that is independently associated with good outcome. As the binary cutoff decreases by 5 mm Hg increments, TWA-MAP first becomes an independent predictor of outcome at 70 mm Hg. A TWA-MAP > 70 mm Hg also has the highest odds ratio for good neurologic outcome at hospital discharge among all thresholds tested.

institution is to leave the decision on whether or not to treat with hypothermia up to the treating clinician.
Pressure (mm Hg) and Vasopressor Use

Column 3 versus column 4, 24% versus 10% (TWA-MAP)

CONCLUSIONS

In this prospective study of post–cardiac arrest patients treated according to consensus recommendations, we found that arterial pressure over the first 6 hours following resuscitation was associated with neurologic outcome. Specifically, we found a threshold effect with a TWA-MAP greater than 70 mm Hg being associated with good neurologic function. Further investigation is warranted to determine if interventions to support blood pressure and promote cerebral blood flow would improve neurologic outcome after cardiac arrest.

REFERENCES


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**TABLE 4. Good Neurologic Outcome Stratified by Time-Weighted Average Mean Arterial Pressure (mm Hg) and Vasopressor Use**

<table>
<thead>
<tr>
<th>TWA-MAP &gt; 70</th>
<th>TWA-MAP &lt; 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Vasopressors</td>
<td>Vasopressors</td>
</tr>
<tr>
<td><strong>n = 54</strong></td>
<td><strong>n = 59</strong></td>
</tr>
<tr>
<td>26 (48)</td>
<td>14 (24)</td>
</tr>
<tr>
<td>0</td>
<td>4 (3–5)</td>
</tr>
</tbody>
</table>

TWA-MAP = time-weighted average mean arterial pressure.

Column 2 versus column 3, 48% versus 24% (p = 0.010 by Fisher exact test).

Column 3 versus column 4, 24% versus 10% (p = 0.442 by Fisher exact test).

Column 3 versus column 5, 24% versus 11% (p = 0.247 by Fisher exact test).
with implementation of a regional cardiac resuscitation center in the United States. Resuscitation 2013; 84:596–601


