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Changes in Expired End-Tidal Carbon Dioxide During Cardiopulmonary Resuscitation in Dogs: A Prognostic Guide for Resuscitation Efforts

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Abstract

Expired end-tidal carbon dioxide (PCO2) measurements made during cardiopulmonary resuscitation have correlated with cardiac output and coronary perfusion pressure when wide ranges of blood flow are included. The utility of such measurements for predicting resuscitation outcome during the low flow state associated with closed chest cardiopulmonary resuscitation remains uncertain. Expired end-tidal PCO2 and coronary perfusion pressures were measured in 15 mongrel dogs undergoing 15 min of closed chest cardiopulmonary resuscitation after a 3 min period of untreated ventricular fibrillation. In six successfully resuscitated dogs, the mean expired end-tidal PCO2 was significantly higher than that in nine nonresuscitated dogs only after 14 min of cardiopulmonary resuscitation (6.2 ± 1.2 versus 3.4 ± 0.8 mmHg; $p < 0.05$). No differences in expired end-tidal PCO2 values were found at 2, 7 or 12 min of cardiopulmonary resuscitation. A significant decline in end-tidal PCO2 levels during the resuscitation effort was seen in the nonresuscitated group (from 6.3 ± 0.8 to 3.4 ± 0.8 mmHg; $p < 0.05$); while the successfully resuscitated group had constant PCO2 levels throughout the 15 min of cardiac arrest (ranging from 6.8 ± 1.1 to 6.2 ± 1.2 mmHg). Changes in expired PCO2 levels during cardiopulmonary resuscitation may be a useful noninvasive predictor of successful resuscitation and survival from cardiac arrest.

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Assessing the efficacy of cardiopulmonary resuscitation during its actual performance is difficult. Common maneuvers such as palpation of a femoral pulse are misleading because such pulses frequently are venous rather than arterial in origin (1). Some investigators (2) have recommended using neurologic signs such as spontaneous movement or intact pupillary reflexes as the only reliable evidence that ongoing resuscitation efforts are effective. This approach, though perhaps quite specific, is far too insensitive for general applicability. To date in experimental models of cardiac arrest, the most reliable method for determining the effectiveness of cardiopulmonary resuscitation is to measure either the aortic diastolic pressure or the coronary perfusion pressure. Coronary perfusion pressure is the diastolic pressure difference between the aorta and the right atrium.

Numerous investigators (3-9) have shown that these two hemodynamic variables correlate very well with measured coronary blood flow during cardiopulmonary resuscitation and with resuscitation outcome. Unfortunately, the need for intraarterial and intraatrial catheters to obtain these measurements makes the routine use of aortic diastolic or coronary perfusion pressure very difficult. Expired end-tidal PCO2 monitoring is a noninvasive alternative technique for inferring blood flow and the potential for successful resuscitation in patients undergoing cardiopulmonary resuscitation (10). When ventilation is held constant, ideally in both rate and tidal volume, the end-tidal PCO2 becomes an excellent measure of pulmonary blood flow. During cardiopulmonary resuscitation, this measure of pulmonary perfusion has been used as a general indicator of resuscitation-generated blood flow.

Expired end-tidal PCO2 in experimental animal models of cardiac arrest has correlated well with cardiac output (11,12), coronary perfusion pressure (13) and resuscitation success (12,14,15) when a very wide range of flow is included. The reliability of expired PCO2 for predicting blood flow and long-term survival within the range of perfusion achievable with standard closed chest techniques of cardiopulmonary resuscitation is less certain. Two recent clinical studies (16,17) have used expired end-tidal PCO2 to monitor patients in cardiac arrest. Neither of these small series showed a difference between survivors and nonsurvivors in expired end-tidal PCO2 levels during cardiopulmonary resuscitation, although both studies emphasized that end-tidal PCO2 increases markedly once spontaneous circulation is restored.

Despite suggestions that expired end-tidal PCO2 levels monitored during cardiopulmonary resuscitation can be useful in guiding therapy, it remains unclear just how reliable such monitoring will be during most clinical resuscitation circumstances. Likewise, no data are available concerning how and when such measurements should be made during cardiopulmonary resuscitation to provide the best information for optimizing therapy. Using a previously described experimental model of cardiac arrest (18,19), we measured expired end-tidal PCO2 levels continuously during standard, closed chest compression, cardiopulmonary resuscitation and fixed rate mechanical ventilation. All surviving animals were followed up for 7 days after resuscitation. Expired PCO2 values obtained during cardiopulmonary resuscitation were retrospectively compared with the final resuscitation outcome for their potential usefulness in predicting longterm survival from cardiac arrest.

Methods

Animal preparation. All animal studies were performed in accordance with the guidelines of the American Physiologic Society and with the approval of the Institutional Animal Care and Use Committees of both Purdue University and the University of Arizona. Fifteen mongrel dogs weighing 23 ± 1 kg were anesthetized with intravenous morphine (2 mg/kg body weight), then endotracheally intubated and maintained on halothane (1 to 1.5%) and oxygen. Once the dogs were anesthetized, the electrocardiogram (ECG) was monitored by means of skin electrodes, and the dogs were instrumented with fluid-filled catheters for measuring ascending aortic and right atrial pressures. Catheter position was determined by both fluoroscopy and characteristic pressure wave forms. Pressure transducers (Microswitch, Gould) measured intravascular pressures that were monitored on a physiologic recorder (Narco-Biosystems). Calibration was accomplished with a mercury manometer. To monitor airway PCO2 concentrations, a Hewlett-Packard 47210A capnometer sensor was attached to the external end of the endotracheal tube after a 30 min warm-up period and internal calibration of the system.

Cardiopulmonary resuscitation protocol. Baseline values including ECG, aortic and right atria1 pressures and airway PCO2 were obtained after halothane was discontinued and while the dog was allowed to spontaneously breathe room air. The depth of anesthesia was thereby lightened until cornea1 reflexes returned and the systemic blood pressure was approximately 120/80 mmHg.

Ventricular fibrillation was induced as previously described (18) by stimulating the left ventricular endocardium with a 60 Hz current. No treatment was performed for the first 3 min of ventricular fibrillation. After this period, standard closed chest compression cardiopulmonary resuscitation was begun with use of a mechanical Thumper (Michigan Instruments, Inc.) programmed according to the American Heart Association standards for basic life support (20). External chest compressions were performed at a rate of 60/min. with a 50% compression-relaxation duty cycle and a 5:1 compression to ventilation ratio. Anterior to posterior chest compressions of 2 in. (5.08 cm) were performed for each dog. Ventilation was provided at a rate of 12/min at a pressure set at 35 cm H_2O through a ventilator incorporated in the mechanical resuscitator. No change in ventilation variables was allowed during the resuscitation period. However, exact ventilatory volumes were not measured. After the 3 min of "downtime," cardiopulmonary resuscitation was performed for a total of 12 min. Epinephrine was administered as a 1 mg intravenous bolus at 10 min of the resuscitation effort. No sodium bicarbonate therapy was given at this time. After 15 min of ventricular fibrillation, electrical defibrillation was attempted with two consecutive 80 J shocks. Dogs with unsuccessful defibrillation received an additional 2 min of closed chest cardiopulmonary resuscitation and then advanced cardiac life support therapy. If ventricular fibrillation persisted. epinephrine (1 mg) and sodium bicarbonate (1 mEq/kg) were administered intravenously and chest compressions continued. If ventricular fibrillation continued, another two defibrillation attempts at 160 J were delivered. Additional closed chest cardiopulmonary resuscitation and another 1 mg of intravenous epinephrine were given when required. Final attempts at defibrillation were then

performed with consecutive shocks of 240 J. Resuscitation efforts were continued until a successful response or the completion of this protocol.

Successful resuscitation was defined as a self-sustained blood pressure ≥ 60/40 mmHg at the end of the advanced cardiac life support period. Successfully resuscitated dogs were given several hours of intensive medical care and were transferred to a maintenance area for 1 week of follow-up care and evaluation. All surviving animals were euthanized at 7 days.

Table 1. Baseline Hemodynamic and Expired End-Tidal Carbon Dioxide (PCO2) Data in 15 Dogs

Group	AoS	AoD	RaS	RaD	CPP	Expired Pco_2
Resuscitated (n=6)	114 ± 7	78 ± 7	3 ± 1	0 ± 1	78 ± 7	45 ± 5
Nonresuscitated (n=9)	108 ± 4	69 ± 3	4 ± 1	1 ± 1	69 ± 3	48 ± 3

All values are in mmHg. AoD = aortic diastolic pressure;
AoS = aortic systolic pressure; CPP = coronary perfusion pressure;
RaD = right atrial diastolic pressure; RaS = right atria1 systolic pressure.

Data and statistical analysis. Data were collected for baseline values just before the 3 min period of untreated ventricular fibrillation. Data were also collected after 2, 7, 12, and 14 min of cardiopulmonary resuscitation. Coronary perfusion pressure was calculated as the aortic mid-diastolic (relaxation phase of chest compression) pressure minus the simultaneous right atria1 mid-diastolic pressure (6-9, 21). Expired end-tidal PCO2 values are reported in millimeters of mercury. Student's t test for unpaired samples was performed for comparing coronary perfusion pressures and expired PCO2 values in the successfully resuscitated and nonresuscitated dogs. One-way analysis of variance was performed to determine any changes in these variables over time. Linear regression analysis was done, comparing coronary perfusion pressure and expired end-tidal PCO2 over the entire time of closed chest cardiopulmonary resuscitation (22). Positive predictive and negative predictive values were calculated (9) to evaluate the premise that an expired end-tidal PCO2 of 6 mmHg, measured at 14 min of cardiopulmonary resuscitation, predicts resuscitation outcome. All data are listed as mean values ± SEM. A p value $p < 0.05$ was considered significant.

Results

Six of the 15 dogs were successfully resuscitated. Five of these six survived the full 7 day follow-up period and were neurologically normal. Nine dogs were not resuscitated. Baseline, prearrest hemodynamic and expired end-tidal PCO2 values showed no differences between dogs that were and were not successfully resuscitated (Table 1).

Expired end-tidal PCO2 (Fig. 1). No differences in expired end-tidal PCO2 values measured during closed chest resuscitation at 2, 7, or 12 min of cardiopulmonary resuscitation were found. However, at 14 min of standard cardiopulmonary resuscitation, the levels of expired end-tidal PCO2 were significantly different between resuscitated and nonresuscitated dogs. A significant decline over the 15 min resuscitation effort in expired PCO2 levels occurred among nonresuscitated dogs (6.3 ± 0.8 versus 3.4 ± 0.8 mmHg; $p < 0.05$, Fig. 1). This was in direct contrast to the PCO2 levels in the dogs that were eventually resuscitated. In these dogs, the level of expired PCO2 remained constant throughout the 15 min of cardiopulmonary resuscitation.

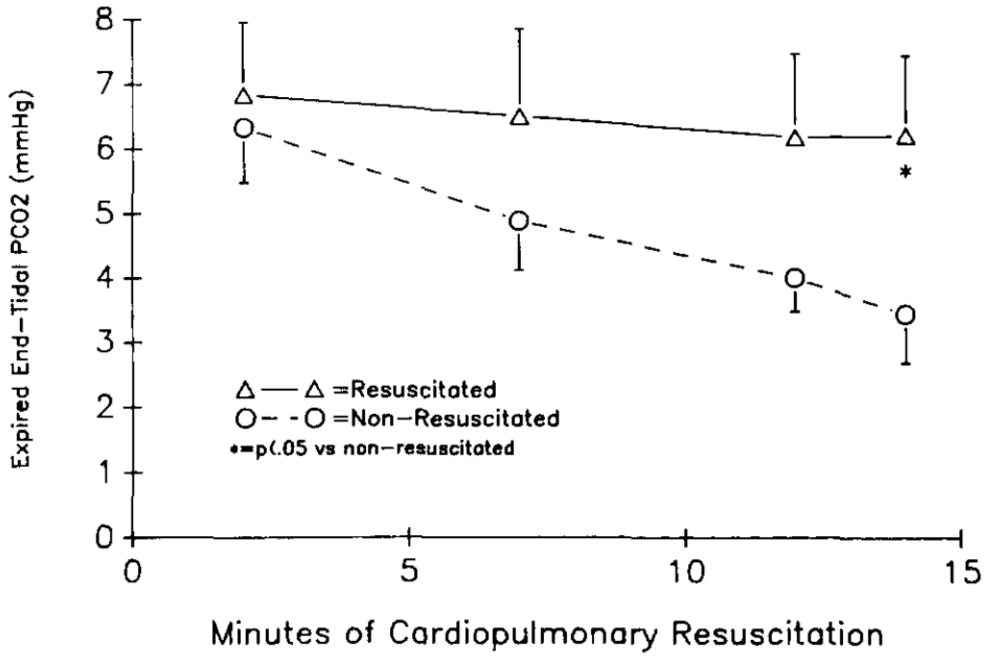

Figure 1. Changes in mean expired end-tidal PCO2 levels over the 15 min of cardiopulmonary resuscitation. No change occurred in dogs that were subsequently resuscitated, but a significant decline was seen in dogs that could not be resuscitated.

Coronary perfusion pressure (Fig. 2). In contrast to expired PCO2, coronary perfusion pressure was significantly greater throughout the majority of the cardiopulmonary resuscitation period among survivors than among nonsurvivors. Only very early in the resuscitation effort, at the 2 min data collection time, did coronary perfusion pressure fail to differentiate dogs that would or would not be resuscitated (Fig. 2). As opposed to the changes seen with expired end-tidal PCO2, which decreased steadily over time in dogs that could not be resuscitated, coronary perfusion pressure did not change over the resuscitation period, though it was consistently poor. However, coronary perfusion pressure among the dogs that were eventually resuscitated increased significantly between 2 and 14 min of cardiopulmonary resuscitation (16.7 ± 1.7 versus 30.0 ± 6.2 mmHg; $p < 0.05$).

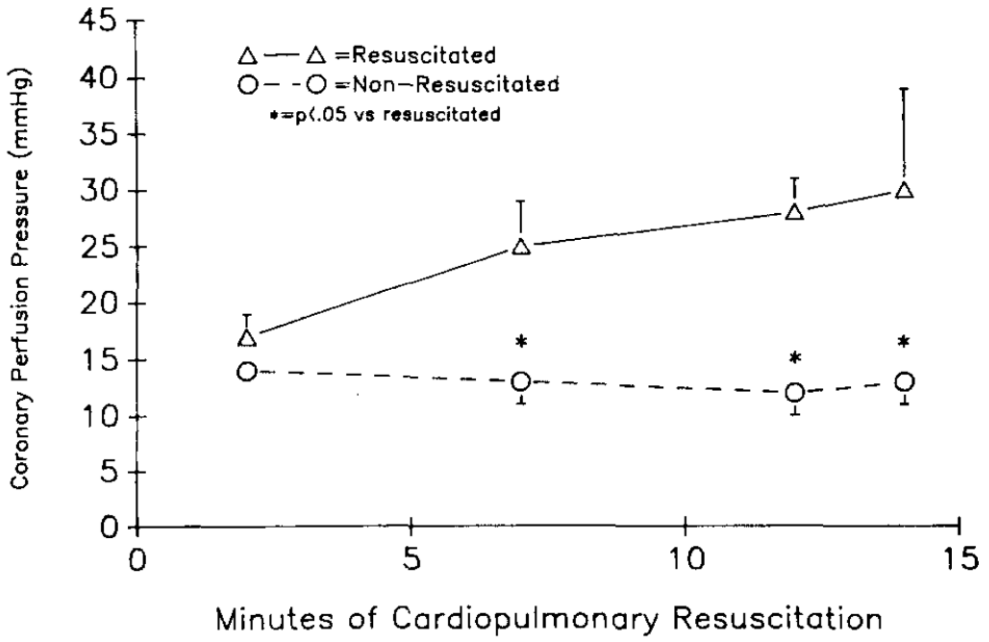

Figure 2. Coronary perfusion pressures for both resuscitated and nonresuscitated dogs. A significant difference between these two groups is seen at 7, 12, and 14 min of cardiopulmonary resuscitation. The dogs that would eventually be resuscitated had an increase in perfusion pressure over the resuscitation period; whereas those that would fail to be resuscitated had no change.

Table 2. Sensitivity, Specificity and Predictive Values of Expired End-Tidal Carbon Dioxide (PCO2) and Coronary Perfusion Pressures

	Sensitivity (TP/TP+FN)	Specificity (TN/TN+FP)	PPV (TP/TP+FP)	NPV (TN/TN+FN)
Early CPR (2 min)				
P_{CO_2}	0.33	0.67	0.40	0.60
CPP	0.50	0.89	0.75	0.73
Late CPR (14 min)				
P_{CO_2}	0.60	0.89	0.75	0.80
CPP	0.80	0.89	0.80	0.89

CPP = coronary perfusion pressure; CPR = cardiopulmonary resuscitation; FN = false negative; FP = false positive: NPV = negative predictive value; PPV = positive predictive value: TN = true negative: TP = true positive.

Predictive value of end-tidal PCO2 (Table 2). Expired end-tidal PCO2 was retrospectively compared with coronary perfusion pressure for positive and negative predictive values for resuscitation outcome. A coronary perfusion pressure > 20 mmHg when measured after 15 min of cardiopulmonary resuscitation has been shown to be an excellent predictor of successful outcome (9). In this study, a coronary perfusion pressure > 20 mmHg after 14 min of cardiopulmonary resuscitation was again found to be a good predictor of successful outcome (positive predictive value of 80%); a coronary perfusion pressure ≤ 20 mmHg was likewise a good predictor of poor expected outcome (negative predictive value of 89%). The positive and negative predictive values of an expired end-tidal PCO2, also measured at 14 min of cardiopulmonary resuscitation, were calculated with use of 6 mmHg as an arbitrarily chosen level for distinguishing between survivors and nonsurvivors. An expired end-tidal PCO2 value r6 mmHg had a positive predictive value of 75%, whereas a value < 6 mmHg had a negative predictive value of 80%.

Expired PCO2 was also compared with coronary perfusion pressure, as has been done previously (13). There was a positive correlation between expired end-tidal PCO2 and coronary perfusion pressure over the range of pressures achieved with standard closed chest compression cardiopulmonary resuscitation ($r = 0.306$; $p < 0.05$).

Discussion

Expired end-tidal PCO2: a noninvasive indicator. Expired end-tidal PCO2 monitoring during cardiopulmonary resuscitation is a potentially useful method for assessing and guiding resuscitation therapy. Unlike aortic diastolic pressure or coronary perfusion pressure measurements, expired PCO2 monitoring is easily performed and requires no invasive catheter placement. Expired end-tidal PCO2 levels during cardiopulmonary resuscitation have correlated with both cardiac output and coronary perfusion pressure in previous reports (11-13). These previous reports included wide ranges of blood flow in establishing good correlation coefficients. The usefulness of expired PCO2 monitoring within the range of pressures and blood flows clinically obtainable with external chest compression was the focus of this study.

Recent clinical reports (16,17) have suggested that monitoring expired end-tidal PCO2 during resuscitation may be a useful guide for assessing effective therapy during cardiopulmonary resuscitation. Garnett et al. (16) found that expired end-tidal PCO2 increased immediately after the return of spontaneous circulation, but they did not find any predictive value for expired PCO2 levels during cardiopulmonary resuscitation in their small clinical trial. Falk et al. (17) recently reported that expired end-tidal PCO2 levels measured during external cardiopulmonary resuscitation in human patients decreased during cardiac arrest and increased with cardiopulmonary resuscitation. They also found no difference in PCO2 between patients who would or would not be resuscitated but noted that PCO2 concentrations could be used to determine when spontaneous circulation had been restored. Gudipati et al. (12) recently showed that expired end-tidal carbon dioxide can predict outcome during cardiopulmonary resuscitation. In a porcine cardiac arrest model in which resuscitation efforts were begun within 1 min of cardiac arrest, resuscitated animals had significantly higher expired end-tidal PCO2 values throughout the 12 min of cardiopulmonary resuscitation than did the nonresuscitated animals. In contrast to our results, they found no decline in expired carbon dioxide levels among animals that would not be resuscitated. The different periods of untreated cardiac arrest preceding cardiopulmonary resuscitation may explain this discrepancy. If more than a few seconds elapse before resuscitation efforts are begun, an accumulation of carbon dioxide may occur. The initial expired end-tidal PCO2 levels seen once cardiopulmonary resuscitation is begun may be relatively high, but they decrease as equilibrium between carbon dioxide production and blood flow is established.

Changes in PCO2 during cardiopulmonary resuscitation. Our data indicate that the usefulness of such monitoring during cardiopulmonary resuscitation may depend on when expired PCO2 is measured during the resuscitation effort. Expired end-tidal PCO2 levels were similar during the first several minutes of cardiopulmonary resuscitation for dogs that were and were not resuscitated. A specific end-tidal PCO2 value measured during these first minutes of resuscitation did not differentiate between those dogs that would do well and those that needed more aggressive therapy. Likewise, at 2 min of cardiopulmonary resuscitation, coronary perfusion pressure also failed to differentiate between dogs that would or would not do well. Over the next 13 min, however, we noted a gradual decline of expired PCO2 in those dogs that

could not be resuscitated (Fig. 2). Thus, the pattern of PCO2 over time may be more significant than one isolated reading.

Predictive value of end-tidal PCO2. The positive and negative predictive values for expired end-tidal PCO2 levels measured later during cardiopulmonary resuscitation were reasonably good. In this animal model, if the expired PCO2 value is 26 mmHg after 14 min of resuscitation therapy, a good outcome can be anticipated. Likewise, if the value is < 6 mmHg, a poor outcome is most likely. Hence, if a PCO2 level of < 6 mmHg is found after 14 min of external chest compressions, more aggressive efforts at resuscitation seem indicated if a successful result is to be expected. This information could be very important in light of new evidence (19,21) that open chest cardiac massage may improve longterm survival after 15 to 20 min of closed chest compressions have been ineffective.

Our study found a much less impressive, nonetheless significant, correlation between expired PCO2 and coronary perfusion pressure than that we reported in the past. In contrast to other reports, this study included only data from standard external cardiopulmonary resuscitation performed in a clinically realistic protocol designed to mimic the everyday performance of basic life support. The range of perfusion pressures was, therefore, narrower than if baseline and postresuscitation values had been included. This narrower range is important because it represents a realistic milieu achievable with standard cardiopulmonary resuscitation. Under the low flow conditions of external cardiopulmonary resuscitation, in which preferential perfusion of the heart and central nervous system may occur, the relations among cardiac output, pulmonary blood flow and myocardial blood flow may be less dependable. Considering the possible variability among isolated expired PCO2 values during standard external cardiopulmonary resuscitation, it appears that monitoring the change in expired PCO2 levels during resuscitation efforts may be the best available method for using this noninvasive technique to predict outcome from cardiac arrest.

Limitations. This experiment was performed in a commonly employed canine cardiac arrest model. However, size and chest configuration are factors that may alter absolute values of airway PCO2 measured during resuscitation in this experimental model compared with humans. Ideally, minute ventilation should be held absolutely constant during the measurement of expired PCO2 if it is to be a true reflection of blood flow. This is difficult in the clinical resuscitation setting. Nonetheless, using this experimental model where ventilatory rate was controlled without measuring minute ventilation, the change over time in expired PCO2 was a useful marker of the effectiveness of cardiopulmonary resuscitation and correlated well with resuscitation outcome after 17 min of cardiac arrest. Further clinical trials using expired end-tidal PCO2 during cardiac arrest and resuscitation therapy are indicated.

Clinical implications. Although it is difficult to extrapolate from experimental work directly to the clinical setting, such experimental data can be very important. We believe that the concept of using end-tidal PCO2 levels during cardiopulmonary resuscitation is valid. We have recently begun a clinical trial, and the preliminary data collected from resuscitation of in-hospital victims of cardiac arrest indicate that by following the current guidelines for resuscitation, ventilation and life support, not only is expired end-tidal PCO2 monitoring easy, but it appears to be of value in identifying patients destined to do poorly. With regard to the ease of measuring end-tidal

PCO2 under clinical conditions, we found that it takes < 3 seconds to connect the capnometer to the endotracheal tube once the patient is intubated.

Conclusion. The value of expired end-tidal PCO2 levels for assessing ongoing external cardiopulmonary resuscitation is dependent on both the quality of cardiopulmonary resuscitation and the time that the measurement is made. Early in the course of resuscitation therapy, PCO2 values did not adequately predict which dogs would be successfully resuscitated. However, over the course of 15 min of resuscitation effort, those dogs that were subsequently unable to be resuscitated had significantly decreased expired PCO2 values. The pattern of expired PCO2, values over the course of resuscitation efforts appears to be a useful prognostic guideline for predicting successful resuscitation and longterm survival.

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