END-TIDAL CARBON DIOXIDE AND OUTCOME OF OUT-OF-HOSPITAL CARDIAC ARREST

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ABSTRACT

Background Survival after cardiac arrest occurring outside the hospital averages less than 3 percent. Unfortunately, the outcome of prolonged resuscitative attempts cannot be predicted. End-tidal carbon dioxide levels reflect cardiac output during cardiopulmonary resuscitation. We prospectively determined whether death could be predicted by monitoring end-tidal carbon dioxide during resuscitation after cardiac arrest.

Methods We performed a prospective observational study in 150 consecutive victims of cardiac arrest outside the hospital who had electrical activity but no pulse. The patients were intubated and evaluated by mainstream end-tidal carbon dioxide monitoring. Our hypothesis was that an end-tidal carbon dioxide level of 10 mm Hg or less after 20 minutes of standard advanced cardiac life support would predict death.

Results There was no difference in the mean age or initial end-tidal carbon dioxide level between patients who survived to hospital admission (survivors) and those who did not (nonsurvivors). After 20 minutes of advanced cardiac life support, end-tidal carbon dioxide ($\pm$SD) averaged 4.4$\pm$2.9 mm Hg in nonsurvivors and 32.8$\pm$7.4 mm Hg in survivors ($P<0.001$). A 20-minute end-tidal carbon dioxide value of 10 mm Hg or less successfully discriminated between the 35 patients who survived to hospital admission and the 115 nonsurvivors. When a 20-minute end-tidal carbon dioxide value of 10 mm Hg or less was used as a screening test to predict death, the sensitivity, specificity, positive predictive value, and negative predictive value were all 100 percent.

Conclusions An end-tidal carbon dioxide level of 10 mm Hg or less measured 20 minutes after the initiation of advanced cardiac life support accurately predicts death in patients with cardiac arrest associated with electrical activity but no pulse. Cardiopulmonary resuscitation may reasonably be terminated in such patients. (N Engl J Med 1997;337:301-6.)

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SINCE Pantridge and Geddes[1] ushered in the current era of advanced cardiac life support by emergency medical personnel, rates of survival to discharge as high as 43 percent have been reported.[2] However, overall survival after out-of-hospital cardiac arrest is more commonly less than 3 percent.[3,4] Higher survival rates have been observed only in patients with ventricular fibrillation who were fortunate enough to have basic and advanced life support initiated early after cardiac arrest. Newer studies reemphasize the importance of these variables but underscore that these factors do not reliably predict survival or death.[5-7] In addition, only a fraction of patients who are initially resuscitated progress to long-term survival. A method of predicting the outcome of cardiac arrest is needed. The end-tidal carbon dioxide level may be a marker that can reliably identify irreversible cardiac arrest.

Normally, levels of alveolar carbon dioxide and therefore end-tidal carbon dioxide are determined by carbon dioxide production, alveolar ventilation, and pulmonary blood flow.[8,9] During low-flow states, end-tidal carbon dioxide levels reflect predominantly pulmonary blood flow; in cardiac arrest, the level is determined entirely by the cardiac output generated by cardiopulmonary resuscitation.[10-18] Therefore, as an indirect measure of cardiac output, end-tidal carbon dioxide represents a potential predictor of survival or death after cardiac arrest.[12-15] Studies to date have focused on predicting survival. We hypothesized that end-tidal carbon dioxide may be more useful as a predictor of death. Therefore, we conducted a prospective study to determine whether quantitative measurement of end-tidal carbon dioxide outside the hospital could be used to predict death in victims of cardiac arrest associated with electrical activity but no pulse.

METHODS

The study community, Whatcom County, Washington, has a population of approximately 160,000, including the city of Bellingham. The initial response to cardiac arrest is provided by emergency medical technicians. Advanced cardiac life support is provided by Whatcom Medic One, a paramedical service based in the Bellingham Fire Department. Response times for advanced life support average less than 4 minutes in the city and less than 10 minutes in the county.

All adults (18 years or more of age) who during the period 1991 through 1995 had primary cardiac arrest associated with electrical activity but no pulse were enrolled in the study (unless they had ventricular tachycardia, ventricular fibrillation, or persistent asystole). Electrical activity without pulse was defined as a wide or narrow electrocardiographic complex of any rate, without the presence of a pulse. Patients with ventricular tachycardia or ventricular fibrillation without pulse were not included in the study because of their more favorable prognosis, but patients with post-defibrillation electrical activity without pulse were included.

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Similarly, patients who converted from asystole to electrical activity without pulse as a result of the initial pharmacotherapy dictated by advanced-cardiac-life-support protocols were included in the study. Patients who remained in asystole despite therapy were excluded. Other exclusion criteria, determined at the initiation of advanced life support, included cardiac arrest due to hypothermia, poisoning, trauma, tension pneumothorax, cardiac tamponade, and hypovolemia.

The paramedics followed standard advanced-cardiac-life-support protocols[16] with on-line medical control from a single base station. The trachea was intubated, and the patient received ventilation with a standard adult, self-refilling bag. The endotracheal tube was immediately connected to a combined pulse oximeter–capnograph (Cosmos, Novametrix Medical Systems, Wallingford, Conn.). End-tidal carbon dioxide analysis was performed by mainstream sampling with a lightweight sensor (Capnostat II, Novametrix) attached directly to the endotracheal tube. The capnograph of this unit works on the principle of nondispersed infrared absorption with dual-wavelength ratiometric single-beam optics. The equipment is self-calibrating; the end-tidal carbon dioxide level and the pattern of the wave form are displayed digitally. End-tidal carbon dioxide data were recorded on a form attached to the patient's emergency-services record.

A persistent end-tidal carbon dioxide level of 10 mm Hg or less after 20 minutes of advanced cardiac life support was chosen a priori as a threshold that would separate patients who did not survive to hospital admission (nonsurvivors) from those who survived to be admitted (survivors), because it represents an extremely low cardiac output over a prolonged period, and in other studies it has been found to be incompatible with life.[12,13,17,18] Unless spontaneous circulation returned, resuscitation continued for at least 20 minutes in all patients. After 20 minutes, it was discontinued if loss of electrical activity (asystole) occurred or restoration of spontaneous circulation was noted. Those who survived to discharge were followed for six weeks after discharge to determine long-term survival and functional status. The study was conducted with the approval of the institutional review board of Whatcom Medic One. The final outcome for all patients was classified as death in the field; restoration of spontaneous circulation in the field, defined as detection of a spontaneous pulse or blood pressure; survival to hospital admission; survival to discharge; or survival six weeks after discharge.

Data are presented as means ±SD. Grouped data were compared by the Wilcoxon rank–sum test. The probability that the association between the 20-minute end-tidal carbon dioxide value and survival to hospital discharge was due to chance was evaluated by Fisher's exact test. Sensitivity, specificity, and positive and negative predictive values were calculated by standard screening-test formulas.[19,20] The null hypothesis was considered to be rejected at a two-tailed alpha rate of 0.05 or less.

RESULTS

One hundred fifty-four patients were considered for the study. Two patients were excluded because postmortem toxicologic studies revealed them to be victims of drug overdose. An additional two patients were excluded; one had a cardiac arrest due to cardiac tamponade and the other had arrest due to hypovolemia.

There was no significant difference in the mean age or initial end-tidal carbon dioxide level between nonsurvivors and survivors to hospital admission (Table 1). After 20 minutes of advanced cardiac life support, end-tidal carbon dioxide levels clearly discriminated between nonsurvivors and survivors, averaging 4.4±2.9 mm Hg (range, 0 to 10) in nonsurvivors and 32.8±7.4 mm Hg (range, 18 to 58)

TABLE 1. END-TIDAL CARBON DIOXIDE VALUES IN PATIENTS WHO SURVIVED TO HOSPITAL ADMISSION AND IN THOSE WHO DID NOT.

VARIABLE	NONSURVIVORS (N=115)	SURVIVORS (N=35)	P VALUE*
	mean ±SD (range)		
Age (yr)	68.0±13.8 (31–95)	71.5±13.0 (27–90)	0.19
End-tidal carbon dioxide (mm Hg)†			
Initial	12.3±6.9 (2–50)	12.2±4.6 (5–22)	0.93
Final	4.4±2.9 (0–10)	32.8±7.4 (18–58)	<0.001

*P values were calculated with the Wilcoxon rank–sum statistic.

†Initial end-tidal carbon dioxide levels were determined immediately upon intubation. Final end-tidal carbon dioxide levels were determined after 20 minutes of advanced cardiac life support.

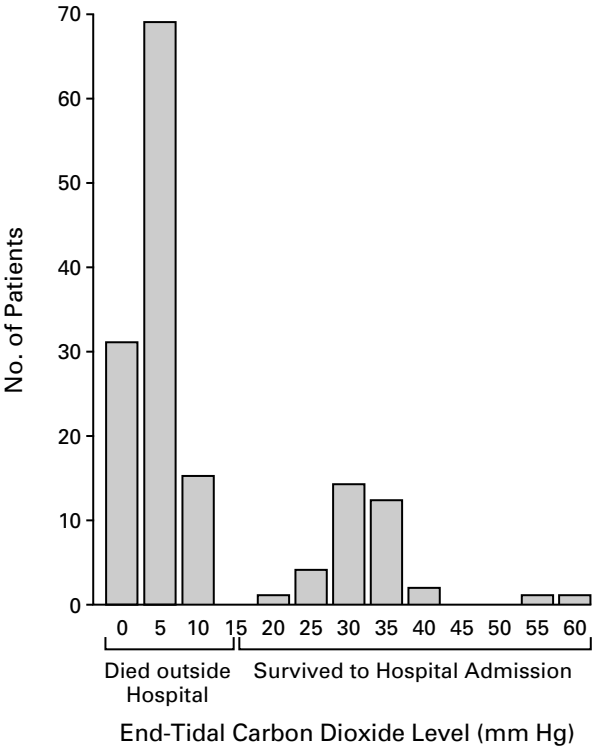

Figure 1. Histogram of Number of Patients (Frequency) at Each Value for End-Tidal Carbon Dioxide, with Standard "Midpoint" Groupings.

The majority of the patients were in the group with end-tidal carbon dioxide levels of 10 mm Hg or less, and all these patients died before reaching the hospital. The frequency distribution clearly differentiates between survivors and nonsurvivors. Values are given as standard midpoint groupings for ease of presentation.

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in survivors ($P<0.001$) (Fig. 1). The results of Fisher's exact test with 20-minute end-tidal carbon dioxide levels dichotomized at 10 mm Hg were also significant ($P<0.001$). An end-tidal carbon dioxide level of 10 mm Hg or less had a sensitivity, specificity, positive predictive value, and negative predictive value of 100 percent. Although the observed survival in the group with a 20-minute end-tidal carbon dioxide value of 10 mm Hg or less was zero in this study, a measure of precision is appropriate for interpreting the estimate. The upper 99 percent binomial confidence limit for the estimated survival is 3.9 percent. This indicates that there is a 99 percent probability that the true survival rate in patients with a 20-minute end-tidal carbon dioxide value of 10 mm Hg or less is no higher than 3.9 percent.

None of the patients with electrical activity but no pulse after 20 minutes of cardiopulmonary resuscitation could be resuscitated. Spontaneous circulation was restored in 35 patients, all within 20 minutes of the initiation of advanced life support. Nineteen of these patients died in the hospital. End-tidal carbon dioxide levels did not discriminate between patients who survived to hospital discharge and those who died in the hospital. Of the 16 patients discharged from the hospital, 14 were alive at six weeks. Eight of these were neurologically intact, five had mild neurologic impairment but were able to care for themselves, and one required skilled nursing assistance. Overall survival to hospital admission was 23.3 percent, and six-week survival was 9.3 percent. Survivors to hospital discharge were younger than those who died in the hospital ($P<0.009$) (Table 2).

TABLE 2. END-TIDAL CARBON DIOXIDE VALUES IN PATIENTS WHO DIED IN THE HOSPITAL AND IN THOSE WHO SURVIVED TO DISCHARGE FROM THE HOSPITAL.

VARIABLE	DIED IN HOSPITAL (N=19)	SURVIVED TO DISCHARGE (N=16)*	P VALUE†
	mean ±SD (range)		
Age (yr)	76.8±6.9 (64–89)	65.2±15.7 (27–90)	0.009
End-tidal carbon dioxide (mm Hg)‡			
Initial	11.9±5.1 (5–20)	12.5±4.1 (7–22)	0.68
Final	31.8±7.3 (18–56)	34.0±7.7 (24–58)	0.28

*Fourteen of these 16 patients were still alive six weeks after discharge from the hospital.

†P values were calculated with the Wilcoxon rank–sum statistic.

‡Initial end-tidal carbon dioxide levels were determined immediately upon intubation. Final end-tidal carbon dioxide levels were determined after 20 minutes of advanced cardiac life support.

DISCUSSION

A small percentage of victims of cardiac arrest are successfully resuscitated and discharged from the hospital. In fact, in most patients who undergo cardiopulmonary resuscitation outside the hospital, spontaneous circulation never returns. Kellermann et al.[21] noted that only 3 of 758 patients transported to a hospital in refractory cardiac arrest were resuscitated, all with moderate-to-severe neurologic deficits. In one hospital, Gray et al.[22] achieved resumption of spontaneous circulation in 16 of 185 patients who could not be resuscitated with advanced cardiac life support outside the hospital. No patient survived to hospital discharge. The cost to the hospital was conservatively estimated at $100,000 to $150,000 for the 169 patients who could not be resuscitated in the emergency department and $180,908 for the 16 patients who were resuscitated but died in the hospital. If these data are extrapolated to the entire United States, the cost of futile resuscitative efforts is estimated at over $1 billion per year.[22,23] Therefore, a marker that could accurately identify victims of cardiac arrest with no chance of survival would save an enormous amount of effort and expense. An increasing body of literature suggests that the end-tidal carbon dioxide level can be used to determine when advanced cardiac life support can be discontinued.

Studies in animals demonstrate excellent correlation between cardiac output and end-tidal carbon dioxide levels in states of low[9,10] and very low[24] cardiac output. In addition, end-tidal carbon dioxide levels accurately reflect cardiac output and the efficacy of cardiopulmonary resuscitation,[25] and they correlate with coronary perfusion pressure and successful resuscitation.[26,27] However, the predictive accuracy of end-tidal carbon dioxide monitoring in patients with cardiac arrest is affected by time. Dohi et al.[28] noted that end-tidal carbon dioxide levels did not reflect pulmonary and systemic circulation in the first minute after cardiac arrest. However, during continued cardiopulmonary resuscitation, end-tidal carbon dioxide levels remained constant in animals that survived but progressively declined in those that could not be resuscitated. In a model simulating pediatric cardiac arrest, Bhende et al.[29] also found that successfully resuscitated puppies maintained an end-tidal carbon dioxide level of 12 mm Hg over 5 to 10 minutes of cardiopulmonary resuscitation. Finally, Kern et al.[30] observed that end-tidal carbon dioxide values could be used to differentiate between survivors and nonsurvivors only after 14 minutes of cardiopulmonary resuscitation.

Studies in humans demonstrate a similar relation among end-tidal carbon dioxide levels, cardiac output, and survival. Falk et al.[15] reported that end-tidal carbon dioxide levels accurately reflected cardiac output in low-flow and no-flow states in 10 patients in an intensive care unit. Two small studies of cardiac arrest outside the hospital[31,32] noted that end-tidal

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carbon dioxide values predicted survival, although another study[11] that measured end-tidal carbon dioxide after a considerable period of cardiopulmonary resuscitation found no correlation. In a more clinically relevant study, Sanders et al.[12] found that the end-tidal carbon dioxide level predicted the success of resuscitation after in-hospital and out-of-hospital cardiac arrest. Resuscitated patients had an average end-tidal carbon dioxide value of at least 10 mm Hg. The difference in end-tidal carbon dioxide values increased over time; at 20 minutes, end-tidal carbon dioxide averaged 18 mm Hg in survivors and 6 mm Hg in those who could not be resuscitated. Although an end-tidal carbon dioxide level of at least 10 mm Hg did not guarantee successful resuscitation, no patient with a value of less than 10 mm Hg was resuscitated.

Callaham and Barton[13] found that the initial end-tidal carbon dioxide level determined after prolonged cardiac arrest and cardiopulmonary resuscitation predicted survival, with values averaging 19 mm Hg in survivors and 5 mm Hg in nonsurvivors. A threshold end-tidal carbon dioxide level of 15 mm Hg had the best sensitivity and specificity, with positive and negative predictive values of 91 percent. However, in four of their resuscitated patients, the initial and later values of end-tidal carbon dioxide were less than 10 mm Hg. Therefore, these authors concluded that since 100 percent sensitivity could not be achieved at a useful level of specificity, a low end-tidal carbon dioxide level was not in itself a sufficient reason to terminate resuscitative efforts. In contrast, Varon et al.[14] found that no patient who survived out-of-hospital or in-hospital cardiac arrest had an end-tidal carbon dioxide level of less than 2 percent (approximately 14 mm Hg).

The effect of improved and new techniques on the ability of cardiopulmonary resuscitation to generate flow, and hence indirectly on the predictive accuracy of end-tidal carbon dioxide monitoring, has also been examined. Investigators have optimized compression[33] and the compression rate[34] in cardiopulmonary resuscitation with end-tidal carbon dioxide monitoring; increased excretion of carbon dioxide correlates with improved cardiac output. However, even with improved technique, Kern et al.[17] found mean end-tidal carbon dioxide levels of 17.9 mm Hg in patients in whom spontaneous circulation was restored and 10.4 mm Hg in those who could not be resuscitated, a threshold not clinically different from the value of 10 mm Hg used in this study. Active compression–decompression cardiopulmonary resuscitation increases end-tidal carbon dioxide[35,36] whereas epinephrine decreases end-tidal carbon dioxide.[37] However, patient survival and the predictive accuracy of end-tidal carbon dioxide levels were not affected by either technique.[38,39] Cantineau et al.[37] noted that no patient with an end-tidal carbon dioxide level of less than 10 mm Hg could be resuscitated.

Despite data supporting an end-tidal carbon dioxide threshold of 10 mm Hg or less as indicative of death in victims of prolonged cardiac arrest, clinicians have been reluctant to incorporate end-tidal carbon dioxide monitoring into advanced cardiac life-support algorithms. This is perhaps because of isolated reports of survivors of lengthy resuscitative efforts who have persistently low end-tidal carbon dioxide values.[13,37] Our study sought to address this issue by studying end-tidal carbon dioxide monitoring in a well-defined, clinically relevant population. The entire study was performed outside the hospital, without introducing variables such as transportation to a new environment. Only cardiac arrest involving electrical activity without pulse was studied, with end-tidal carbon dioxide monitoring initiated at the time resuscitation began.

As expected, restoration of spontaneous circulation was achieved early in the experimental period if it occurred at all. However, the key finding of this study is that circulation was never restored in any patient with persistent electrical activity but no pulse after 20 minutes of advanced life support. This is not surprising given the prolonged, severe insult that was documented by an end-tidal carbon dioxide level of 10 mm Hg or less at the end of the 20-minute interval. We also noted that the difference between the end-tidal carbon dioxide levels of survivors and nonsurvivors increased over time. By using a threshold of 10 mm Hg measured after 20 minutes of advanced cardiac life support to determine whether death (rather than survival) could be predicted, we found both sensitivity and specificity to be 100 percent.

Our data strongly suggest a threshold effect between 10 and 18 mm Hg of end-tidal carbon dioxide. No patient who had an end-tidal carbon dioxide level of less than 10 mm Hg survived. Conversely, in all 35 patients in whom spontaneous circulation was restored, end-tidal carbon dioxide rose to at least 18 mm Hg before the clinically detectable return of vital signs.

The difference between survivors and nonsurvivors in 20-minute end-tidal carbon dioxide levels is dramatic and obvious, and extensive analyses are not necessary to demonstrate it. Future studies are needed to demonstrate that the findings are reproducible, however. Among the patients in whom spontaneous circulation was restored, end-tidal carbon dioxide levels did not discriminate between long-term survivors and those who died in the hospital. Therefore, end-tidal carbon dioxide is useful as a predictor of death in patients with cardiac arrest who have electrical activity but no pulse. However, it cannot be used to determine which of the patients in whom spontaneous circulation is restored will be long-term survivors.

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This study had several potential limitations. Our data were derived from a well-defined population with pulseless electrical activity. Other dysrhythmias and patient populations need to be studied before our conclusions can be extended to other patients with cardiac arrest. However, as we have noted, reports of end-tidal carbon dioxide monitoring in various animal and patient populations support our hypothesis that a threshold value of end-tidal carbon dioxide exists, below which the likelihood of survival is zero. We believe that until these data can be extended to all types of cardiac arrest, a conservative approach should be maintained by using an end-tidal carbon dioxide level of 7 mm Hg, for example, as reason to discontinue cardiopulmonary resuscitation after 20 minutes of advanced cardiac life support. Use of this criterion would greatly reduce the number of patients with cardiac arrest who undergo prolonged, futile resuscitative efforts in the field and in the hospital, resulting in substantial savings of money and health care resources.

Finally, although several states permit the discontinuation of resuscitative efforts outside the hospital, many do not. Therefore, legislative changes may be required for the guidelines suggested by this study to be implemented.

CONCLUSIONS

This study demonstrates that the level of end-tidal carbon dioxide measured during resuscitative efforts can be a predictor of death from cardiac arrest in patients with electrical activity but no pulse. Measuring end-tidal carbon dioxide is technically feasible outside the hospital, and the results can be used to determine when advanced cardiac life support can be discontinued, decreasing the efforts and costs entailed in futile resuscitative efforts. If future studies of outside-the-hospital and in-hospital cardiac arrest confirm the accuracy of this marker in patients with electrical activity but no pulse and in those with other dysrhythmias, changes can be made in American Heart Association protocols to allow the discontinuation of resuscitative efforts when they are no longer of value to the patient.

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