Selected Controversies in Cardiopulmonary Resuscitation

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ABSTRACT

Cardiopulmonary resuscitation (CPR) is performed frequently by paramedics, emergency department personnel, and inpatient physicians. Unfortunately, after more than 40 years of practice and study, there are still many controversies and unresolved treatment issues. This article focuses on four current controversies in CPR: (1) the role of end-tidal CO$_2$ (ETCO$_2$) detection, (2) the use of bicarbonate, (3) whether epinephrine is the optimal alpha agonist, and (4) whether amiodarone should replace lidocaine as the initial antiarrhythmic of choice in the treatment of ventricular fibrillation.

KEYWORDS: Cardiac arrest, CPR, amiodarone, vasopressin, ETCO$_2$, capnography, ventricular fibrillation, epinephrine

Objectives: Upon completion of this article, the reader will appreciate the essential nature of end tidal CO$_2$ (ETCO$_2$) monitoring in airway management, review the appropriate use and nonuse of bicarbonate during cardiopulmonary resuscitation, learn about the potential role of alpha agonists other than epinephrine in managing pulseless rhythms and make a value judgment on which alpha agonist is optimal for restoring a perfusing rhythm, and understand the new role of amiodarone in cardiac resuscitation.

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ETCO₂ Measurement
The end-tidal gas is the last few milliliters of gas expired from the alveoli.¹ It is least diluted by the nonventilated air spaces of the bronchioles and larger airways, and as such, best reflects the milieu of the alveoli, and in turn, the alveolar capillary bed. Because CO₂ is present at negligible concentration in room air (0.03%), devices that measure ETCO₂ detect only CO₂ produced as a by-product of cellular metabolism. That is, they only detect CO₂ that is absorbed by the tissue capillary beds and delivered via the pulmonary circulation to the alveolar capillary beds where the CO₂ is then expired through intact airways. Therefore, measurement of ETCO₂ requires that all components are intact including cellular metabolism, a functional circulation, working lungs, and patent airways. If the patient is intubated, it also requires a correctly located ETT. ETCO₂ is usually reported as either percent (%) or torr, with 1% equaling approximately 7 torr. Normally, ETCO₂ averages 4 to 5% (28 to 35 torr).

Several types of ETCO₂ measuring devices are commonly available:²

1. Colorimetric ETCO₂ detectors (eg, EasyCap and PediCap [Nellcor, Hayward, CA]): These are inexpensive (< $20), lightweight, disposable semi-quantitative devices that are attached in-line between a ventilating source (e.g., bag-valve-mask or mechanical ventilator) and an ETT connecting to each by standard 22mm ID and 15mm ID connectors, respectively. An integrated pH sensitive chemically impregnated filter paper reacts to CO₂ and yields a reliable color change, with graduations from: purple or “A” reading equating to a PCO₂ < 4 torr or < 0.5%; an intermediate brownish color or “B” reading, which indicates a PCO₂ of 4 to 15 torr or 0.5 to < 2%; to a yellow or “C” reading indicating a PCO₂ of 15 to 38 torr or 2 to 5%. The relatively large deadspace (38 mL) in the adult version (EasyCap) precludes use in children weighing less than 10 kg. The pediatric version (PediCap) can be used in children weighing 1 to 15 kg; however, because of increased airway resistance imparted by the smaller size, the pediatric device should not be used in adults or in spontaneously breathing intubated infants. The reversible colorimetric reaction is stable for 2 hours when these devices are exposed to air, but exposure to humidified gases (e.g., aerosol treatments) will decrease functionality to 20 to 30 minutes. It is important to be aware that if the filter paper becomes exposed to acid (e.g., gastric contents/vomitus or epinephrine injected via the ETT), the paper will turn and permanently remain yellow.

2. Capnometer: These devices are more costly ($750 to > $1000) but are reusable so that the per use cost is similar to the disposable devices. They are generally amenable to use in children and adults, although dead-space issues may limit use in infants. An infrared beam at 4.3 µm, the wavelength uniquely absorbed by CO₂ is passed through the expired gas stream, and the decrease in the amount of transmitted energy is measured.¹,³ The exhaled gas can be sampled as it is passes out the ETT (mainstream), or an aliquot can be aspirated and analyzed separately (sidestream). Capnometers yield a numerical value for the measured CO₂. The highest value in any breath is the ETCO₂.

3. Capnograph: Similar technology to capnometer, but also incorporates time-flow graphing function to give additional information about pulmonary and cardiovascular function. Characteristic waveforms can identify different pathology, although the interpretation of such waveforms is beyond the scope of this discussion. The presence of an easily read characteristic waveform, however, does confirm an intact delivery system of CO₂ breath by breath.

CONFIRMATION OF ENDOTRACHEAL TUBE POSITION
The “gold-standard” for determining correct ETT positioning is assumed by many to be visualization of the ETT traversing the vocal cords. This standard makes two assumptions: (1) that the cords can be adequately visualized during the entire intubation process, including final tube passage, and (2) that the intubator can always see vocal cords despite variations in patient anatomy and pathology. Because during emergency intubations it is frequently not possible to completely or adequately visualize tube passage,⁴⁻⁶ other means to verify ETT position must be employed.

Meticulous clinical assessment of ETT position has been advocated by many instructional sources, including numerous textbooks for medical and paramedical personnel.⁶⁻⁷ Such clinical assessment routinely includes (1) listening for breath sounds, anteriorly and in the axillae, (2) listening for absence of breath sounds over the epigastrium, (3) observing for condensation within the ETT, and (4) observing for chest rise and absence of abdominal distention. Clinical assessment however has been shown in many studies to miss an unacceptable number of esophageal intubations, even by skilled airway managers.⁵⁻⁸⁻¹¹ In one study, axillary breath sounds were interpreted as normal by anesthesiologists or anesthetists in 6 of 40 (15%) operating room
patients intentionally intubated in the esophagus.\textsuperscript{9} Epigastric movement was interpreted as normal in 36 (90\%) of the patients. In addition, tube condensation, considered by many to be a reliable sign of correct intratracheal placement, occurred in 85\% of the esophageal tubes.

Experience certainly plays a role in the reliability of clinical assessment. In a controlled study of critical care unit patients who each had an ETT in both the esophagus and the trachea, experienced critical care physicians (> 4 years) using chest and epigastric auscultation were able to detect 100\% of 78 esophageally placed ETTs, whereas senior medical students incorrectly identified esophagus as tracheal in 10 of 78 trials (13\%).\textsuperscript{10} Relative inexperience and overreliance on clinical assessment may be significant factors in out-of-hospital intubation mishaps. Pelucio et al reported 1 to 3 unrecognized esophageal intubations per 40 to 60 patients (1.6\% to 7.5\% miss rate) as performed by approximately 120 paramedics in the Washington, DC, area.\textsuperscript{11} Of note, the frequency of intubation for each paramedic averaged only 1 intubation every 2 or 3 months, a frequency that would make the development of proficiency difficult, if not impossible.

ETCO\textsubscript{2} detection has been proven to be extremely reliable in ensuring that an ETT tube has not been inadvertently placed into the esophagus.\textsuperscript{3,5,12-15} In tens of thousands of uses, there have been no published reports, in either anesthesia, critical care, or emergency medicine literature, of properly used ETCO\textsubscript{2} devices incorrectly indicating tracheal placement, when in fact the tube was inserted into the esophagus. One prehospital study did note an esophageal tube placement in a victim of cardiac arrest, despite “color change” on a colorimetric ETCO\textsubscript{2} detector and clinical signs of correct tube placement.\textsuperscript{15} However, the degree of color change was not noted, nor was it documented that the color change was maintained after 6 ventilations. The authors of that study postulate that the ETT migrated to the esophagus prior to position confirmation in the ED.

There are three situations that may allow false-positive ETCO\textsubscript{2} readings in nontracheal intubated patients: (1) Poorly performed bag-valve-mask ventilation may allow sufficient expired CO\textsubscript{2} to be ventilated into the stomach. (2) Carbonated beverages could have recently been consumed to cause detection of CO\textsubscript{2} from an esophageally placed ETT.\textsuperscript{16} The volume of CO\textsubscript{2} in either case is such that it will be “washed out” after 3 to 6 tidal breaths. On a colorimetric detector, the color would likely be in the “B” range initially, decreasing to the “A” range by the seventh delivered breath.\textsuperscript{13} Capnographs and capnometers would show a similar degradation in values to near-zero. (3) A falsely high ETCO\textsubscript{2} reading can also occur when the ETT tip is too shallow, in the hypopharynx, in which case there is enough gas exchange to cause tracheal range CO\textsubscript{2} readings without degradation and with similar waveform to a tracheally placed tube.\textsuperscript{14} This almost always occurs during blind nasotracheal intubations.

Although ETCO\textsubscript{2} detectors are excellent in determining ETT location in a well-perfused, well-ventilated patient, they may be problematic in shocky patients and during cardiac arrests. Low levels of expired CO\textsubscript{2} may occur because of pulmonary hyperperfusion as a result of systemic hypoperfusion, as seen in cardiac arrest, or as a result of V/Q (ventilation/perfusion) mismatch as in massive pulmonary embolism. In approximately 20 to 30\% of cardiac arrest victims, CO\textsubscript{2} levels are too low to be detected by colorimetric detectors\textsuperscript{3,13,15} in these situations capnometers and capnographs are more discriminating.\textsuperscript{3} Falsely low levels may also occur when the cuff of the ETT is not inflated sufficiently and expired air escapes preferentially around the ETT because of increased resistance imparted by the detector. In such cases, the clinician may incorrectly assume that the tube is errantly placed in the esophagus.

If ETCO\textsubscript{2} detectors are so effective in ensuring that esophageal intubation does not go unrecognized, why does this potentially devastating error continue to occur? We believe that pride, stubbornness, and failure of instructors to stress the inaccuracy of physical exam findings all contribute to this problem. Wayne et al noted a dramatic decrease in documented unrecognized esophageal intubation after instituting mandatory capnography use; the sole failure was one case in which EMS personnel chose to ignore the lack of end-tidal capnographic waveform.\textsuperscript{17}

**SUMMARY OF ETCO\textsubscript{2} USE IN EMERGENCY AIRWAYS**

Some form of ETCO\textsubscript{2} monitoring is required in every operating room in the United States. The American College of Emergency Physicians has endorsed the use of ETCO\textsubscript{2} detection for emergency department intubations.\textsuperscript{18} The National Association of State EMS Directors has also issued a policy statement supporting the routine use of such devices for every out-of-hospital intubation.\textsuperscript{19} We believe that it is now time to incorporate ETCO\textsubscript{2} detection as a core concept within the training curricula of standard resuscitation courses, such as the Advanced Cardiac Life Support course. Years and years of teaching clinical assessment have imparted a bias that is costing lives. This bias can be overcome by exposing a larger provider base to standards that are based on the routine use of this life-saving technology.

**Use of ETCO\textsubscript{2} Monitoring in Cardiac Arrest**

ETCO\textsubscript{2} has been shown to change logarithmically with cardiac output.\textsuperscript{20} At normal levels of cardiac output, ventilatory function determines ETCO\textsubscript{2} with values approximating those of arterial CO\textsubscript{2} tension (PaCO\textsubscript{2}). When cardiac output falls below 50\% of normal, CO\textsubscript{2}
delivery becomes rate-limiting, and the pulmonary blood flow becomes the primary determinant of the ETCO₂ level. As a consequence, changes in ETCO₂ will directly reflect changes in cardiac output.¹

During cardiac arrest with closed-chest cardiopulmonary resuscitation (CPR), cardiac output is usually only about 20 to 30% of normal.²¹ Given that lung ventilation is unchanged or even increased during CPR, the diminished mount of delivered CO₂ is very effectively removed from the alveoli. This results in high venous CO₂ levels (because of low pulmonary blood flow), very low alveolar CO₂ and ETCO₂ levels (because of decreased delivery coupled with very efficient alveolar washout), and low PaCO₂ (because of maximal transcapillary CO₂ extraction from increased contact time between alveolar capillaries and alveolar gas space). If circulation is restored, the CO₂-rich venous blood can offload even more CO₂ than normal, resulting in a sudden increase in measured ETCO₂ at return of circulation. This spike in ETCO₂ has been observed to herald restoration of circulation even before clinical signs of reperfusion are evident.²²⁻²⁴

It has long been known that ETCO₂ levels may stay nearly unmeasurable during a resuscitation. This observation was first noted in 1929 by Rudolf Eisenmenger as he was performing early experiments measuring expired CO₂ during resuscitation. Koetter provides a translation of Eisenmenger from German: “If during a resuscitation attempt the analysis of the expired air, performed about twice per hour, still shows plenty of carbon dioxide, then continuation of artificial respiration [and circulation] would be indicated. If, however, a sharply declining CO₂ elimination in expired air is found, or even more a cessation of CO₂ elimination, then further attempts are futile.”²⁴

The futility of prolonged out-of-hospital resuscitation efforts has been well studied. In a large prospective study of 1068 victims of nontraumatic out-of-hospital cardiac arrest, Kellerman et al found only 3 survivors to discharge in the 768 patients in whom restoration of circulation was not accomplished in the field by EMS personnel.²⁵ The three survivors all experienced arrest after EMS arrival and all had severe neurologic disability. Sixty-nine percent of the patients who did develop a return of circulation, however, survived to hospital admission, 26.5% survived to hospital discharge, and 19% survived with no or only mild neurologic deficits. In contrast, only 7% of the patients who were not successfully resuscitated by EMS were admitted. Other studies have yielded similar dismal results when out-of-hospital efforts were unsuccessful.²⁶⁻²⁷

It follows, then, that ETCO₂ monitoring, a sensitive indicator of return of circulation, could be used to monitor for the lack thereof, and so could be used to determine nonresuscitability. Callaham and Barton prospectively evaluated ETCO₂ levels of 55 patients who arrived in the ED (Emergency Department) in arrest.²⁸ ETCO₂ was measured on arrival, and a receiver-operator curve developed for likelihood of return of spontaneous circulation. A threshold level of 15 torr would discriminate between those patients with and without return of circulation, with positive and negative predictive value of 91%. However, the authors noted successful resuscitations in 4 patients with ETCO₂ levels persistently below 10 torr. Survival to discharge and long-term outcome were not explored. In a small out-of-hospital study of 25 cardiac arrest patients, Entholzer et al reported 3 of 7 successful resuscitations in patients who averaged less than 10 torr;²² again, survival to discharge was not reported.

Other human studies have not demonstrated survival when ETCO₂ levels persistently averaged below 10 torr. Sanders et al studied 35 patients who had ETCO₂ monitoring during in-hospital cardiac arrests; 9 were resuscitated with 3 survivors to discharge. None of the patients who had ETCO₂ values averaging less than 10 torr were successfully resuscitated.²⁹ All who failed resuscitation had a steady decline of ETCO₂ over time; those who were successfully resuscitated tended to have steady ETCO₂ or a gradual increase over time. Levine, et al, prospectively evaluated 150 out-of-hospital cardiac arrest victims.³⁰ Patients were included if they had electrical activity without pulse, but were excluded with ventricular fibrillation/pulseless ventricular tachycardia or asystole unless they deteriorated to PEA (pulseless electrical activity) rhythm. Patients found to have reversible causes of PEA (hypovolemia, tension pneumothorax, pericardial tamponade) were also excluded. ETCO₂ was measured at 20 minutes of resuscitation, with a theoretical decision to discontinue resuscitation if ETCO₂ measured less than 10 torr. None of the 115 patients who had persistent PEA and ETCO₂ less than 10 torr after 20 minutes of advanced cardiac life support (ACLS) were successfully resuscitated. Thirty-five patients achieved return of circulation within 20 minutes; of those, 14 patients survived to 6-week follow-up, and 13 had no or minor neurologic disability.

Colorimetric ETCO₂ detector can also be utilized to better define patients who are unlikely to survive to hospital admission.³¹ In 144 uses of the colorimetric ETCO₂ detector in arrested patients, all 24 (17%) who survived to hospital admission had colorimetric readings in the “B” or “C” range (4 to 38 torr). Conversely, none of the 41 arrest patients who had continued “A” readings (< 4 torr) with confirmed tracheal intubation and epinephrine were resuscitated.

**Conclusion on ETCO₂ Use in Discontinuing CPR**

We believe that ETCO₂ should play an adjunctive role in the management of cardiac arrest. Along with judgment about the adequacy and duration of resuscitation
efforts, persistent ETCO₂ levels below 10 torr provide additional justification for discontinuance of resuscitative efforts. ETCO₂ monitoring may also provide early indication of return of circulation that might otherwise go unrecognized because of CPR artifact effects on either the heart monitor or pulse palpation. In addition, ETCO₂ monitoring may help identify patients with subclinical perfusion (pseudo-PEA), in whom more prolonged resuscitation may be warranted. In patients with profound hypothermia who appear to be pulseless with a perfusing rhythm (in whom increased tissue turgidity hampers clinical detection of a pulse), routine use of ETCO₂ monitoring may identify patients in whom CPR is not needed, avoiding the risk of compressing irritable myocardium. Finally, ETCO₂ monitoring may provide feedback about the adequacy of CPR, permitting the rescuer to optimize his or her compression technique and timing.

Summary
We believe the ETCO₂ detectors should be required for all emergency intubations whether performed in the field, the ED, or an inpatient area. ETCO₂ detectors allow more definitive confirmation of tracheal placement of the ETT. Continued ETCO₂ measurement during CPR also allows a better assessment of cardiac output and the presence or lack of adequate perfusion. Those pulseless patients in asystole or PEA who persist with no, or very low, levels of ETCO₂ after intubation and multiple doses of epinephrine, should usually have their resuscitations terminated after 10 to 20 minutes.

BICARBONATE USE IN CARDIOPULMONARY RESUSCITATION
Over the past 3 decades, the use of many drugs during CPR has been evaluated and reevaluated. One such drug is sodium bicarbonate. Although its use was once heavily favored, it is no longer routinely recommended unless a preexisting acidosis is present. It is now controversial as to whether sodium bicarbonate should be used at all during CPR, even if a preexisting acidosis is present, such as in septic shock or diabetic ketoacidosis (DKA).

A number of studies have been conducted attempting to show sodium bicarbonate’s potential benefits. During the early 1960s, several studies stating its benefits appeared. It was widely assumed that a profound metabolic acidosis was present during cardiac arrest and that sodium bicarbonate was indicated prior to epinephrine administration to reverse the acidosis of cardiac arrest. Anderson, et al attempted to demonstrate that sodium bicarbonate use during cardiopulmonary arrest reversed acidosis and that its use would be beneficial. They evaluated cardiac output in 23 dogs in whom a metabolic acidosis was induced. The study demonstrated that cardiac output only declined when the pH fell below 6.9, and that the response to epinephrine was maintained to a level as low as pH of 6.8. The authors, however, concluded that patients undergoing CPR have extreme degrees of acidosis, and that the prompt administration of an alkylating agent such as bicarbonate was the standard of practice without a pH determination.

Several animal studies also demonstrated that bicarbonate administration during cardiopulmonary arrest improved cardiac output and increased fibrillatory threshold. Of note however, was that bicarbonate’s benefits were only seen when the pH was below a level of 6.8 to 7.0. Based on these early studies, it was expected that proof of bicarbonate’s benefits would emerge as more rigorous studies using increasingly modern techniques were performed. This has not however been the case.

In the early 1990s, Sanders and colleagues attempted to better define sodium bicarbonate’s role during CPR. They performed CPR on 21 mongrel dogs with, and without, bicarbonate and fluid administration. This study was designed so that all animals received mechanical ventilation, and had their oxygenation and perfusion ensured during CPR. This well-done study demonstrated that (1) the acidosis of early cardiac arrest is respiratory in nature and that a severe acidosis does not exist in well ventilated patients; (2) no significant acidosis exists during early CPR if there has been good ventilation and chest compressions; (3) sodium bicarbonate may actually cause a significant alkalosis in well-ventilated and well-perfused animals; in these animals, pH values as high as 7.55 were seen when 4 to 6 mEq/kg of sodium bicarbonate was administered and finally; (4) although sodium bicarbonate increases pCO₂, serum osmolarity and pH, its use does not affect outcome or mean arterial pressure.

The main reason that sodium bicarbonate does not appear to be beneficial or indicated during CPR is related to the type of acidosis present in low and no flow states. Multiple studies have demonstrated that the acidosis seen in the low flow-no flow state of early cardiac arrest is predominantly a respiratory acidosis. During CPR the cardiac output is roughly 25 to 30% of normal, and accumulation of CO₂ in tissues occurs due to decreased clearance of CO₂ secondary to reduced blood flow. It is only late into the arrest, well after 20 minutes of pulselessness, that a combined metabolic and respiratory acidosis exists. Because sodium bicarbonate administration generates CO₂, it would not be expected to improve the predominant respiratory acidosis in most cardiac arrests.

Sodium bicarbonate’s ability to significantly elevate CO₂ levels has been demonstrated in humans. The main reason that sodium bicarbonate does not appear to be beneficial or indicated during CPR is related to the type of acidosis present in low and no flow states. Multiple studies have demonstrated that the acidosis seen in the low flow-no flow state of early cardiac arrest is predominantly a respiratory acidosis. During CPR the cardiac output is roughly 25 to 30% of normal, and accumulation of CO₂ in tissues occurs due to decreased clearance of CO₂ secondary to reduced blood flow. It is only late into the arrest, well after 20 minutes of pulselessness, that a combined metabolic and respiratory acidosis exists. Because sodium bicarbonate administration generates CO₂, it would not be expected to improve the predominant respiratory acidosis in most cardiac arrests.
Weil and colleagues evaluated 16 critically ill patients during cardiopulmonary arrest. Patients received an average dose of 130 (± 30 mEq) of sodium bicarbonate over a median interval of 23 minutes, while their arterial and venous pH, pCO₂, and serum bicarbonate values were compared. After receiving bicarbonate during CPR, these 16 patients had an average arterial pH of 7.41, however, their venous pH was markedly lower at 7.15. Similarly, the arterial pCO₂ was 32 mmHg, but was 74 mmHg on the venous side. There were no significant differences in the serum bicarbonate concentrations on the arterial versus the venous side with values of 25 mmol/L and 23 mmol/L, respectively (p < 0.001). Thus, although sodium bicarbonate may improve arterial pH, it causes a paradoxical increase in the respiratory acidosis throughout the rest of the body. This study supports the concept that the arterial and venous systems exist almost like two separate compartments during the low flow state of CPR.

In 1995, Dybvik and colleagues published the only prospective randomized clinical trial evaluating sodium bicarbonate’s role during cardiopulmonary arrest. This Norwegian study involved 502 patients with out-of-hospital arrest over a 5-year period and examined outcome when normal saline was compared to a special hypertonic buffer mixture including sodium bicarbonate. No difference in return of spontaneous circulation or hospital discharge was observed between the two groups, and there was a trend toward better survival in the saline group. The authors concluded that buffer therapy did not affect the resuscitability or outcome after out-of-hospital cardiac arrest.

A recent evidence-based review of sodium bicarbonate’s role during CPR critically reviewed 3 decades of animal and human studies. Studies were divided into animal or human, and the human studies were sub-divided into five levels: level I studies—randomized controlled trials; level II studies—small nondefinitive randomized controlled trials; level III—prospective cohort studies; level IV—case control studies; and level V—a cohort or case series study. Surprisingly, there were no level I studies performed over the past 3 decades. There was only one level II study by Dybvik, which showed no difference in outcome with sodium bicarbonate administration during CPR. Of nine prospective level III studies, five showed no difference, and four showed deleterious effects including mortality or worsening of outcome measures. There were six case control level IV studies, five of which showed no difference, and one, which demonstrated a deleterious effect. Finally, there were four level V studies, three of which showed deleterious effects, and one of which demonstrated no difference in outcome with sodium bicarbonate administration during CPR.

This evidence-based review noted that many of the earlier studies were retrospective reviews with no control groups, and that conclusions drawn from these early studies were not based on outcomes and that no human study has demonstrated a beneficial impact on survival. Finally, eight human studies and numerous animal studies have demonstrated detrimental effects including impaired myocardial function when bicarbonate is administered during CPR.

Based on all of the available information, bicarbonate is clearly not indicated in the management of the typical patient suffering a cardiac arrest. If bicarbonate is administered to patients who are being well ventilated and receiving proper manual CPR, it may either induce a metabolic alkalosis and/or generate increased CO₂ on the venous side and create, or worsen, a respiratory acidosis. The only question that remains is whether bicarbonate should be administered to any specific patient type if they suffer a cardiac arrest. Specifically, should bicarbonate be used in cardiac arrests in hyperkalemic patients, those with a Tricyclic Antidepressant (TCA) overdose, those in DKA, or those patients who develop a profound metabolic acidosis due to high lactate levels such as cardiac arrest after status seizures?

Special CPR Circumstances in Which Sodium Bicarbonate Should Be Considered

HYPERKALEMIA

Hyperkalemia is the most dangerous acute electrolyte abnormality. Elevated serum potassium may cause ventricular ectopy, a wide complex QRS that may degenerate into a sine wave or ventricular fibrillation (VF). In the past, sodium bicarbonate therapy was considered a mainstay for treating any hyperkalemic patient regardless of etiology or the patient’s serum pH. Androge and Madias in 1981 reviewed 44 studies involving serum potassium during acute acid-base disturbances. The authors noted that sodium bicarbonate had quite variable effects in affecting serum potassium values depending on whether the patient was acidic or had a normal serum pH. Additionally, in acidic patients sodium bicarbonate administration had different effects in metabolic versus respiratory acidosis. Sodium bicarbonate only had a potassium lowering effect in patients who had an underlying metabolic acidosis. Only in these acidic patients did sodium bicarbonate decrease serum potassium and assist in stabilizing the patient hemodynamically. These results have been replicated by others.

Thus, although sodium bicarbonate has a limited role in hyperkalemia, its role in hyperkalemic cardiac arrest seems relatively clear. Although there are many causes of hyperkalemia, the most common cause of life-threatening hyperkalemia is chronic renal failure in patients with an underlying metabolic acidosis. Pa-
patients with renal failure who suffer hyperkalemic-induced cardiac arrest should initially receive calcium chloride, 10 to 20 mL intravenously, in an attempt to stabilize the myocardium. Sodium bicarbonate at an initial dose between 1 and 1.5 mEq/kg should be administered in conjunction with glucose and insulin. Both the sodium bicarbonate and glucose-insulin administration should drive potassium intracellularly. The patient’s pH should be brought toward 7.2 to 7.3, and hemodialysis should be initiated as quickly as possible in those cardiac arrest patients who respond to initial medical therapy.

**TCA OVERDOSE**

Tricyclic antidepressants (TCA) and related compounds are one of the most common causes of death in overdose patients presenting to the emergency department. Although TCAs prolong the Q-T interval and may cause torsade de pointes ventricular tachycardia (VT), their major cardiotoxic effect is produced by blocking sodium channels and depressing the ventricular conducting system. Tricyclic antidepressants depress conduction by poisoning the sodium channels and delaying depolarization of the myocardium. This slowing of phase 0 depolarization results in a widened QRS complex. At present, bicarbonate administration appears to be the best way to overcome this sodium channel blockade. Bicarbonate administration and the resultant metabolic alkalosis may also decrease the toxic effects of tricyclic antidepressants by decreasing the amount of free drug in the serum. Increasing the serum pH from 7.4 to 7.55 decreases the amount of active drug by 55 to 66%.

Several studies have demonstrated bicarbonate abilities to immediately correct TCA-induced hypotension, QRS widening, Q-T interval prolongation, and ventricular arrhythmias. The reversal of toxicity is seen in patients who are acidic, have a normal pH, or have a preexisting respiratory alkalosis. Sasyniuk and colleagues demonstrated that sodium bicarbonate effectively reversed ventricular arrhythmias caused by TCA intoxication. Cardiac Purkinje’s fibers were exposed to amitriptyline (500 ng/mL) and perfused with either a sodium bicarbonate solution, a high sodium solution, or a high pH, low pCO2 solution. Although all three solutions produced an improvement of phase 0 abnormalities, the magnitude of improvement was significantly greater after the administration of sodium bicarbonate ($p < 0.05$).

Because the terminal event in most TCA overdoses is cardiovascular collapse due to poisoning of the sodium channels, bicarbonate administration seems appropriate in TCA overdose arrests. The only exception being those cardiac arrests due to a prolonged Q-T interval. We believe bicarbonate is indicated in patients who (1) deteriorate, or arrest, with a QRS greater than 100 msec, (2) a sine wave, or (3) develop hypotension refractory to saline. A minimum of 100 mEq of sodium bicarbonate should be rapidly infused by bolus administration and the patient’s pH should be elevated to approximately 7.55. Clinicians must be aware that aggressive sodium bicarbonate administration should not occur in patients who are also being hyperventilated. Sodium bicarbonate has no role in a TCA-induced torsades de pointes arrest where magnesium is the drug of choice.

**DIABETIC KETO ACIDOSIS**

Theoretically, bicarbonate should be very beneficial in the treatment of DKA. Based on data from the physiology laboratory coupled with animal and human data, it was believed bicarbonate could improve insulin sensitivity, improve cardiac and pulmonary function, decrease the work of breathing, decrease malignant arrhythmias, and reduce the duration of coma. Multiple studies, however, have failed to show any benefit from bicarbonate in DKA and have suggested its use may actually be detrimental.

In theory, bicarbonate therapy in DKA should allow pH to rise more rapidly and for metabolic homeostasis to be regained sooner. However, because bicarbonate is hyperosmolar, high in sodium, generates CO2, and may change serum pH rapidly, multiple potential deleterious effects are possible. These include volume overload, hypokalemia, metabolic alkalosis, decreased O2 delivery to tissues, and delayed recovery from ketoacidosis. Because CO2 rapidly crosses the blood-brain barrier but bicarbonate does not, both a paradoxical CSF acidosis and cerebral edema are possible. This is most likely due to the rapid rise in CSF pCO2 concentrations without a concomitant rise in CSF bicarbonate.

In an early series, Lever and Jaspan reported on 95 episodes of DKA. They found no significant difference in a rate of pH rise or glucose fall in the 73 episodes of DKA treated with bicarbonate as compared with the 21 cases where no bicarbonate was administered. Similar results in conjunction with a similar antacidic message were reported by Morris and colleagues evaluating 21 patients randomized to varying doses of bicarbonate based on pH (6.9 to 7.14) versus no bicarbonate.

A potential deleterious effect of bicarbonate administration was reported by Okuda et al, who placed 7 patients on low dose insulin drips. Three patients received 44 to 50 mEq/hour for 4 hours. Bicarbonate-treated patients took an extra 6 hours to clear all organic acids. A 1998 retrospective review of 147 cases of DKA in 109 children under 16 years of age also suggests another disadvantage of bicarbonate administration. Although there were no differences in complications or rate of HCO3 and pH rise in patients who received bi-
carbonate versus those who did not, the length of hospitalization was 1 day longer in patients receiving bicarbonate.

Based on no proven efficacy and many potential dangers, bicarbonate is not appropriate in most cases of DKA. However, DKA patients who suffer a cardiac arrest during their initial phase of therapy will likely have pH values below 6.9, which has been the lower limit of case series that have evaluated bicarbonate’s effects. We recommend 2 ampules (88 to 100 mEq) of intravenous bicarbonate be administered by IV bolus in patients who arrest during initial therapy for DKA. Their profound acidosis and likely concomitant hyperkalemia should benefit from buffer therapy. As soon as the patient has been intubated and the bicarbonate has circulated for 1 to 2 minutes, subsequent therapy should be based on obtaining an arterial pH of 7.1 to 7.2.

LACTIC ACIDOSIS

One of the most controversial uses of sodium bicarbonate involves its use in lactic acidosis. It was believed that a low pH in patients was harmful because it impaired the cardiovascular system, and that sodium bicarbonate could be used to increase the pH and improve both the cardiovascular function and decrease morbidity and mortality.33–35,56 Scientific study, however, has not supported bicarbonate’s benefits. Studies performed on human ventricular muscle displayed only modestly reduced contractility in the face of severe acidosis.57 More importantly, several studies involving patients with lactic acidosis receiving vasoactive drugs and sodium bicarbonate demonstrated that, although sodium bicarbonate did raise the serum pH and bicarbonate concentrations, it did not improve hemodynamics or catecholamine responsiveness.38,59 Additionally, a number of studies have actually demonstrated a decrease in the intracellular pH with the administration of sodium bicarbonate.56,60

The role of sodium bicarbonate in the treatment of lactic acidosis has recently been reviewed by Forsythe and Schmidt.51 They reviewed multiple studies that used either nuclear magnetic resonance, fluorescent dye, or dimethylxolazolidine to demonstrate bicarbonate’s deleterious effects in lowering intracellular pH. The authors reviewed more than 90 publications and concluded that bicarbonate has no proven benefit in lactic acidosis, even in patients with pH levels below 7.2 or those refractory to pressor therapy.

We recommend that bicarbonate only be used in severe lactic acidosis that results in cardiac arrest. Most specifically, acute lactic acidosis from such toxins as methanol, ethylene glycol, isoniazid, and aspirin. Patients should have their pH values acutely raised to approximately 7.0 to 7.1 in an effort to maximize the chance of a successful resuscitation. If a perfusing rhythm can be reobtained, then the patient’s pH should be raised to normal in these cases of a toxin-induced metabolic acidosis.

Conclusion on Bicarbonate Use in CPR

Bicarbonate has no role in most cardiac arrests. It probably has a role however in those patients who arrest due to specific toxins and metabolic abnormalities. Patients who suffer a cardiac arrest due to hyperkalemia, DKA, or a tricyclic antidepressant overdose, or who develop acute lactic acidosis from status seizures, aspirin, methanol, or ethylene glycol, should benefit from bicarbonate administration. Without good evidence against its use in these specific situations, we feel there is good logic in recommending its selective use.

IS EPINEPHRINE STILL THE PRESSOR OF CHOICE IN CPR?

The goal of pharmacological intervention in cardiac arrest is the restoration of spontaneous circulation. The ideal agent should reestablish an adequate spontaneous circulation and blood pressure, optimize cardiac function, and preferentially shunt blood toward vital organs. The ideal agent should also balance the oxygen demands and supply of the heart and increase coronary perfusion pressure, and should not promote arrhythmias.

Epinephrine

For the last 30 years, the primary agent used in CPR has been epinephrine.62 First shown to be useful in cardiac resuscitation in 1906 by Crile and Dolley,63 epinephrine is a naturally occurring catecholamine that is a nonselective stimulator of both alpha- and beta-adrenergic receptors and is one of the most potent vasopressors known.32 Its primary alpha effects include increasing systemic vascular resistance, increasing blood pressure, and enhancing contractile force. Animal models suggest that epinephrine’s alpha-adrenergic stimulation causes more systemic vasoconstriction than cerebral or myocardial vasoconstriction, thus enhancing circulation to these vital organs.64 Epinephrine increases coronary artery blood flow and myocardial perfusion due to its ability to raise end-aortic diastolic pressure.64,66 Epinephrine thus appears to have a beneficial effect on myocardial blood flow despite causing a degree of coronary vasoconstriction.64,66 The increase in myocardial blood flow while also inducing systemic vasoconstriction may be the key to epinephrine’s efficacy in restoring spontaneous circulation.65

Epinephrine is a very potent beta-agonist. Its primary beta1 actions include increasing the force and rate of contractions (positive inotropy and chronotropy) and increasing AV nodal conduction velocity (automaticity). Its beta2 actions are less important in cardiac
resuscitation and relate to the relaxation of smooth muscle.\textsuperscript{64,66} Although initially felt to be an important attribute, it is no longer widely held that the beta-adrenergic effects of epinephrine enhance defibrillation.\textsuperscript{64}

Although it has been the cornerstone of ACLS for many years, epinephrine’s efficacy as the best agent in cardiac resuscitation from pulseless rhythms has begun to be questioned.\textsuperscript{64,67–69} Despite the fact that epinephrine can restore spontaneous circulation, there is a very low rate of survival to hospital discharge in CPR victims.\textsuperscript{67} Additionally, the rate of discharge of neurologically intact survivors is abysmally low with typical survival rates reported in the range of 5 to 6%.\textsuperscript{67–71} Several studies have even shown a trend toward worse outcomes with the use of epinephrine when compared with the nonuse of epinephrine in both the prehospital and inpatient cardiac arrest populations.\textsuperscript{67,69} In a relatively large study of 773 patients suffering in-hospital arrests, no association between the use of ACLS drugs and improved outcomes could be found.\textsuperscript{67} In fact, the use of epinephrine, atropine, bicarbonate, or calcium was associated with worse outcomes. The use of higher dose epinephrine (0.1 mg/kg to 0.2 mg/kg) has also not been promising in adult cardiac arrest.\textsuperscript{70,71}

It has been postulated that, whereas epinephrine’s alpha effects on peripheral resistance are responsible for the restoration of circulation, epinephrine’s beta effects are responsible for its adverse effects.\textsuperscript{63,66} Several animal studies have shown that the beta effects of epinephrine are quite deleterious in that the damaged heart has excessive demands placed on it by beta\textsubscript{1}-driven increases in inotropy and chronotropy. This unbalances myocardial oxygen demands and supply leading to further myocardial ischemia and predisposes the heart to fibrillation.\textsuperscript{63,72} Studies where animals were given a beta-blocker as well as epinephrine had higher resuscitation rates when compared with epinephrine alone, epinephrine plus an alpha-blocker, or epinephrine plus alpha- and beta-blockade.\textsuperscript{66,73} Therefore, many authors have suggested that epinephrine might not be the ideal drug for cardiac arrest.

Although it must be emphatically stated that the literature does not support the discontinuance of the use of epinephrine, there are many studies that suggest there are other agents that may be preferentially employed. The first alternative would be to look at other alpha-agonists.

**Alpha-Agonists in CPR**

Norepinephrine, which differs from epinephrine in structure only by the deletion of a methyl group on the terminal amine, is almost as potent an alpha-agonist as epinephrine. Due to differences in its interaction with beta-receptors, norepinephrine raises peripheral vascular resistance to a much greater degree than epinephrine.\textsuperscript{74} Whereas this is useful in refractory shock states like sepsis, it may also decrease cardiac output and have a negative effect on cerebral blood flow. The use of the synthetic catecholamine dopamine has also been advocated due to its significant alpha activity at high doses, but its efficacy has not been proven equivalent to that of epinephrine.\textsuperscript{75,76}

The use of pure alpha-agonists was suggested as early as the 1960s.\textsuperscript{77} Several animal studies demonstrated that the pure alpha-one agonist methoxamine was at least as efficacious as epinephrine.\textsuperscript{77,78} Roberts et al showed that methoxamine produced higher cerebral and myocardial blood flows during canine CPR, and this might lead to the higher survival rates and improved cardiac function in the methoxamine-treated group.\textsuperscript{78} However, a randomized human trial of witnessed cardiac arrest victims failed to show any difference between epinephrine and methoxamine in survival rates or neurologic outcome.\textsuperscript{79} Multiple studies have also shown the benefit of using another pure alpha-agonist, phenylephrine,\textsuperscript{63,80} but there are no definitive human studies to show its superiority over epinephrine.

**Aminophylline**

There is growing recognition of the role adenosine plays in the failing heart. Adenosine is a breakdown product of adenosine triphosphate (ATP) during ischemia and does appear to have a cardioprotective role. It has negative chronotropic, inotropic, and dromotropic effects, and it has been theorized that during prolonged ventricular fibrillation states, excessively high levels of adenosine may play a significant role in postcardioversion asystole and electromechanical dissociation.\textsuperscript{81,82} The methylxanthine aminophylline is a known adenosine antagonist, and there have been anecdotal reports of its successful use in refractory arrest.\textsuperscript{82} However, animal studies by two different groups of researchers failed to show any improvement in the return of spontaneous circulation or 1-hour survival.\textsuperscript{81,82} Additionally, one study actually showed a trend toward worse outcomes with the use of aminophylline in a canine heart model of ventricular fibrillation.\textsuperscript{81} Finally, one randomized human prehospital trial also failed to show any benefit from the addition of aminophylline to the standard ACLS protocol.\textsuperscript{83}

**Vasopressin**

Another agent that is the subject of much recent interest is vasopressin. Vasopressin is an exogenous form of antidiuretic hormone (ADH) that stimulates vascular smooth muscle in addition to its primary effect on free water reabsorption in the kidney.\textsuperscript{84–86} Lindner et al discovered that there are very high concentrations of circulating endogenous vasopressin in patients undergoing
CPR, and that successfully revived patients had higher levels of vasopressin than unsuccessfully revived ones.84 Because higher levels of circulating vasopressin correlated with improved outcome, researchers have attempted to determine whether this agent could have a beneficial role in cardiac arrest. Pig heart studies of both ventricular fibrillation and pulseless electrical activity have demonstrated an improvement in vital organ blood flow in vasopressin-treated animals versus those treated with epinephrine.85–87 Lindner et al showed that high dose vasopressin (0.8 U/kg) was superior to epinephrine in improving coronary perfusion pressure and myocardial blood flow during ventricular fibrillation.85 Another group of researchers also found that repeated doses of vasopressin could maintain this level in a prolonged cardiac arrest model, whereas only the initial dose of epinephrine could.65 Finally, vasopressin has been shown to have a beneficial effect on cerebral blood flow88 and has shown improved neurologic survival in animals.88

Several human studies have also suggested there is a role for vasopressin. In a small study, Morris et al showed that 40% of patients had an improvement in coronary perfusion pressure after vasopressin administration following a prolonged arrest.89 Epinephrine however did not improve coronary perfusion pressure in any of the 10 subjects. Lindner et al used 40 units of arginine vasopressin intravenously in resuscitating 8 in-patients that had failed standard ACLS measures.90 Although all 8 had an initial return of spontaneous circulation and 3 were discharged from the hospital neurologically intact, it must be noted that none of the 3 survivors suffered an ischemia-related arrest, and the sample size was too small to draw any definitive conclusions. This same group followed up their original vasopressin study with a randomized double blind study comparing the efficacy of vasopressin (40 U) and epinephrine (1 mg) in out-of-hospital arrests secondary to ventricular fibrillation.91 The vasopressin group fared better in terms of initial resuscitation, survival to admission, and survival to discharge.

Although some of the above studies are encouraging, there is still much research needed to be performed before there is any alteration in the standard ACLS protocol. Large, multicenter trials are needed to determine the true efficacy and the proper dose of vasopressin. The correct dose is unknown, as only one dose of vasopressin (40 U) has ever been studied in humans. The side effects of vasopressin are well known, and the effects of high doses on myocardial performance and peripheral circulation in human subjects must be considered before adopting its widespread use.

Conclusion on Epinephrine in CPR
Although it is unclear whether epinephrine is the optimal pressor to restore spontaneous circulation and maximize neurologic recovery, no other pure or mixed alpha agonist or other pressor has demonstrated superiority. Until such studies appear, the 1.0 mg dose of epinephrine utilized by Redding and Pearson in the early 1960s is still the drug of choice for the early 2000s.

SHOULD AMIODARONE REPLACE LIDOCAINE IN ACLS ALGORITHM FOR VENTRICULAR FIBRILLATION?
Lidocaine has been the primary antiarrhythmic of choice in the treatment of ventricular fibrillation (VF) since the American Heart Association (AHA) first began promulgation of its ACLS algorithms.32 As we begin the year 2001, the AHA is revising its protocols and will replace lidocaine with amiodarone as its initial antiarrhythmic of choice in VF. Because there is a significant chance for long-term survival in patients who suffer a VF arrest, the best possible protocol for reversing this often fatal arrhythmia is essential.92,93

Survival after cardiac arrest has remained dismal for the past quarter century. Although the ACLS protocols have been revised numerous times as new medications have been released, survival from cardiac arrest is unlikely unless a patient is rapidly defibrillated out of VF or pulseless VT.32,92,94 With the exception of improving response times to defibrillation and the more widespread use of automatic and semiautomatic external defibrillators, no newer antiarrhythmic had improved survival after a VF arrest.93,95 Thus the publication in 1999 of a relatively large study demonstrating amiodarone could cause a 29% increase in survival to hospital admission after a VF arrest has excited many and led the AHA to reconsider how to pharmacologically treat VF and pulseless VT.95

This section discusses the best approach to VF and focuses on whether amiodarone should replace lidocaine in the VF algorithm. Background on amiodarone and the recent Arrest Trial will be provided; lidocaine’s effectiveness in VF is evaluated as are two other commonly used antiarrhythmics, bretylium and procainamide. This section concludes with a recommendation on how to resolve the amiodarone versus lidocaine controversy.

Amiodarone
Amiodarone is an antiarrhythmic that affects all portions of the action potential. Its effects on prolonging repolarization (phase III) are felt to be its most dominant mechanism of action.95 It does, however, have sodium channel-blocking effects (phase 0), prolonging the rate of rise of the action potential; it lengthens depolarization (phase II), and depresses spontaneous depolarization (phase IV).93,96 It also has weak beta-blockerlike effects and is considered an antifibrillant.93 Since its release in the mid-1980s, it has been an effective antiarrhythmic for refractory supraventricular and
ventricular arrhythmias. It has been shown to be effective in 50 to 70% of patients with malignant ventricular arrhythmias that were refractory to multiple other medications.96

Amiodarone’s potential role to replace lidocaine in the initial therapy of VF is based on reports of its effectiveness where lidocaine has failed. Nalos and colleagues administered intravenous amiodarone to 22 patients with VT refractory to lidocaine.97 Twenty of 22 had also failed to respond to procainamide and 18 of 22 had failed bretylium. Amiodarone at a loading dose of 150 mg or 300 mg was effective during this short in-hospital study in terminating recurrent VT in 16 of 22 patients. Their results were consistent with an earlier German study in which amiodarone controlled recurrent VF or VT in 9 of 15 patients who had failed multiple other antiarrhythmics.98

Based on the cited studies and other confirmatory reports of amiodarone’s effectiveness, a randomized clinical trial entitled The ARREST trial was performed.99 This study was designed to assess the efficacy of amiodarone in electrically resistant out-of-hospital VF and pulseless VT. Eligible patients had VF/VT that had not responded to three defibrillation attempts. Patients then received 1.0 mg of intravenous epinephrine and were randomized to 300 mg of IV amiodarone, or only its diluent, polysorbate 80, as a placebo. Following the blinded randomization, patients were shocked at 360 ws; those who continued in VF/VT then received standard ACLS medications, typically beginning with lidocaine.

The results of the study are very impressive when comparing the rates for hospital admission in the amiodarone group with those of the standard ACLS group. Of the 504 patients randomized: 44% (108 of 246 patients) of the amiodarone treated patients were admitted to the hospital with a perfusing rhythm as compared to 33% (89 of 258 patients) in the standard ACLS group; a difference of 29% (p = 0.03). There was some increase in side-effects utilizing amiodarone, including a 16% absolute increase in hypotension and a 30% increase in bradycardia, but this did not compromise amiodarone’s overall benefits. Noteworthy also, is that the average number of shocks in both groups was 5 ± 2, and approximately the same number of patients in both groups received additional antiarrhythmic drugs for VF/VT (66% of the amiodarone group vs 73% of the standard ACLS group; p = 0.13).

The most important measure of a cardiac arrest medication’s efficacy is its ability to allow patients to survive neurologically intact. Although there was a 29% increase in hospital admissions utilizing amiodarone, there was no benefit as measured by an improvement in survival to discharge. Unfortunately, whether measured by percent or absolute numbers, there was no increase in survival until hospital discharge in the amiodarone treated patients (33 amiodarone patients vs 34 ACLS patients; 13.4% vs 13.2% respectively). Of note, this lack of difference also applied to likelihood of a survivor being neurologically intact (18/33 amiodarone survivors vs 17/34 standard ACLS survivors).

Before deciding whether amiodarone should replace other antiarrhythmics, it is important to review the efficacy and limitations of lidocaine, bretylium, and procainamide in VF.

Lidocaine

Lidocaine has always been a first-line agent for VF/VT.32,92 There are, however very few human studies that provide strong support for lidocaine’s efficacy. Lidocaine is a class 1b antiarrhythmic agent that raises the ventricular fibrillatory threshold and prolongs the refractoriness in ischemic myocardium, while shortening the action potential in nonischemic areas.1,99,100

Although lidocaine has traditionally been considered by most to be the drug of choice for both preventing and treating VF and VT, numerous studies have questioned its efficacy.101–103 Based on multiple studies of its lack of proven efficacy and its potential to cause seizures and asystole, lidocaine is no longer recommended prophylactically in patients with myocardial infarction.104 Lidocaine’s efficacy in treating malignant ventricular arrhythmias has also been questioned because numerous studies have shown it to be relatively ineffective.105,106

Armengol et al evaluated lidocaine’s role in 20 patients with wide QRS tachycardias, 17 of whom had VT.105 Lidocaine worked in only 6 of the 31 wide complex tachyarrhythmias these patients had. Similar results were obtained in a recent study by Gorgels et al.106 In this study lidocaine terminated only 4 of 15 episodes of monomorphic VT.

Lidocaine’s effectiveness in VF is not well documented, though there are some retrospective and prospective studies that have attempted to evaluate its role as an ACLS medication. Harrison reported on 116 patients who had shock resistant VF and who could have received lidocaine if a base station physician had chosen to order it.103 In 62 patients (53%), physicians requested paramedics administer 100 mg of lidocaine; in 54 patients (47%), no lidocaine was ordered. The results of this study showed no significant differences in patients still in VF on ED arrival (45% vs 46%) or patients admitted to the CCU (21% vs 17%). Although not statistically significant, more neurologic survivors came from the lidocaine-receiving group: 7 patients (11%) versus 1 patient (2%).

Similar nonsupportive results have been reported by others. In a retrospective study attempting to evaluate all of the commonly used ACLS medications, Van Walraven, Stiell, and colleagues were unable to show a definitive benefit in VF resuscitation rates due to lidocaine.67 The authors did note that survivors of resuscitations due to any rhythm were more likely to have re-
ceived lidocaine, though the difference was not statistically significant. Lack of effectiveness of lidocaine was similarly shown in a retrospective study comparing three successive defibrillations for VF versus administering lidocaine between the first and second defibrillation attempts. Resuscitation rates were higher in those patients who had not had lidocaine interrupt their defibrillation sequence (30% vs 19%).

In a recent Swedish prehospital care study, lidocaine’s efficacy was evaluated retrospectively in 290 patients who sustained VF. In the 185 patients who received lidocaine, 45% had return of a pulse and 38% were admitted to the hospital; as compared to a 24% return of pulse and 18% hospitalization rate for those who did not receive lidocaine ($p < 0.001$; $p < 0.05$, respectively). However, despite more than a doubling of the hospitalization rate, lidocaine therapy was not associated with a statistically significant increase in survival to discharge (lidocaine 14% vs no lidocaine 8%; $p = $NS).

There have been prospective studies evaluating lidocaine’s effectiveness in VF that compared lidocaine to another antiarrhythmic, bretylium. There have not been any prospective trials comparing lidocaine to procainamide in VF; however, there are data from studies comparing these two agents in VT.

**Bretylium**

Bretylium is a class 3 agent and is often referred to as an antifibrillant. Unlike lidocaine, bretylium lowers the defibrillation threshold. Multiple studies have attempted to compare bretylium’s efficacy to that of lidocaine. Unfortunately, the methodology of these studies resulted in many patients receiving both bretylium and lidocaine during their resuscitations. Each agent however, was often effective after the other had initially failed. The combined use of both drugs has been suggested because they may be synergistic, one may work when the other has failed, and bretylium’s onset of action may be delayed whereas lidocaine’s is immediate. Of interest, amiodarone has also been compared to bretylium in unstable VT and VF. This study of 302 patients compared infusions of the drugs over a 48-hour period. The study demonstrated similar effectiveness for bretylium and amiodarone though there was more hypotension due to bretylium (33% vs 20%).

Prior to making recommendations on whether amiodarone should replace lidocaine as the primary ACLS drug for VF, one other ventricular antiarrhythmic needs mention. Many patients with VT who have not responded to lidocaine do respond to the class 1a antiarrhythmic procainamide. In the study in which lidocaine only converted 7 of 15 episodes of monomorphic VT, procainamide converted 20 of 26 episodes. Additionally, procainamide converted 8 of 11 patients in whom lidocaine had failed.

**Summary of the Data on Antiarrhythmics**

Based on the above data, a few concepts emerge: (1) amiodarone has dramatically improved success from defibrillation and admission to the hospital in one relatively large prospective study of patients in VF; (2) lidocaine’s efficacy is unproven, yet it has been the traditional ventricular antiarrhythmic since the ACLS course began, and it has facilitated conversion from VF including cases in which bretylium has failed; (3) bretylium’s efficacy is also unproven, yet it has facilitated conversion from shock resistant VF including cases in which lidocaine failed; (4) procainamide seems to be far superior to lidocaine in VT; (5) finally and most importantly, no antiarrhythmic agents including amiodarone, lidocaine, bretylium or procainamide has ever been shown to definitely improve survival from shock resistant VF.

**CONCLUSION**

Based on the above premises, a rational approach to resolve the controversy of whether amiodarone should replace lidocaine initially appears somewhat intuitive. Because amiodarone requires a 10 cc-flush of the IV line to avoid thrombophlebitis, (or dilution to 20 cc), lidocaine administration at a dose of 1 to 1.5 mg/kg (approximately 10 cc) could immediately follow amiodarone administration. This would avoid making a qualitative judgment on which drug is superior and could help to avoid polarizing and confusing clinicians, nurses, and prehospital care providers. Unfortunately, there appears to be a significant increase in asystole when these two agents are combined. Therefore, based on the results of the ARREST Trial, clinicians should switch to amiodarone as the preferred first-line agent in VF. This recommendation is based on the results of only one trial. However, lidocaine has not proven its efficacy over the past quarter century. Although the evidence is not conclusive, it favors a switch to the newer and more promising amiodarone. More information will be forthcoming in the next 36–48 months. Until then, we believe the ACLS recommendation for amiodarone’s first-line antiarrhythmic status is appropriate.

**REFERENCES**

25. Kellerman AL, Hackman BB, Sones G. Predicting the outcome of unsuccessful pre-hospital advanced cardiac life support. JAMA 1993;270:1433–1436
41. Kuvin JT. Electrocardiographic changes of hyperkalemia. NEJM 1998;338:662