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Controversial Issues in Cardiopulmonary Resuscitation

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CONTENTS

CARDIOPULMONARY RESUSCITATION (CPR) has been the subject of both anecdotes and descriptive research studies, which have resulted in an important step forward in medicine. Unfortunately, few attempts have been made to dispute the dogma surrounding aspects of the physiology and drug management of CPR. Indeed, since the advent of CPR in 1960 when external chest compressions were described by Kouwenhoven and Jude at The Johns Hopkins Hospital until very recently,[1] the techniques and theories behind its use went unquestioned.

A number of questions and controversies about the physiology and pharmacology of CPR have arisen in the last few years (table 1). For example, it is still not well understood why blood flows during CPR. As new information appears regarding mechanisms of blood flow, there is hot debate over how clinical guidelines for chest compressions should be altered. Anatomic differences between infants, older children, and adults that affect their responses to CPR have just begun to be addressed. Again, the effect of these findings on clinical practice is yet to be determined. In addition, many researchers are investigating the effects of drugs such as calcium blockers on vital organ blood flow during ischemia, and the results of these studies may affect our practice of advanced CPR. New information regarding glucose metabolism and acid-base factors during ischemia may also alter the clinical practice of CPR.

In fact, a number of changes were made in the American Heart Association's recommendations for CPR in 1986.[2] These changes addressed both mechanical and pharmacological aspects of CPR. For example, the number of chest compressions per minute have been increased for adults from 60 to a minimum of 80 and preferably 100 per minute. This change is consistent with both the cardiac pump and thoracic pump theories of blood flow during CPR. Changes have been made also in recommendations covering the indiscriminate use of sodium bicarbonate and calcium chloride. For CPR in children, hand position for chest compressions has been altered to

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Key words: Brain: blood–brain barrier; blood flow. Cardiopulmonary resuscitation: abdominal counterpulsation; chest compliance. Heart: coronary blood flow. Ions: calcium. Metabolism: glucose. Pharmacology: calcium channel blocking drugs. Sympathetic nervous system: epinephrine; phenylephrine.

TABLE 1. Controversial Issues in CPR

- Mechanics
  - Mechanisms of Blood Flow
    - direct cardiac compression
    - intrathoracic pump mechanism
      - age differences
  - Use of Newer Techniques
    - SCV CPR
    - Vest CPR
    - Abdominal Compressions
- Drugs
  - Adrenergic Drugs
    - Epinephrine *versus* alpha-adrenergic agonists
  - Bicarbonate—use or overuse?
  - Glucose
  - Calcium or calcium-channel blockers

conform with the true anatomy of the child. All of these changes are discussed below in greater detail. We have not attempted to write an exhaustive repetition of the Standards and Guidelines of Cardiopulmonary Resuscitation and Emergency Cardiac Care,[2] but to critically review the literature in order to elucidate some of the controversial issues of clinical CPR.

Animal and Human Physiology

Differences between human physiology and that of other species need to be closely addressed if animal studies of CPR are to be interpreted correctly. The compliance and geometry of the chests of various species differ greatly from those of the human chest, and these differences affect mechanical maneuvers needed to generate blood pressure during CPR. For example, the chest of many breeds of dogs is keel-shaped, so that chest compression in the anterior-posterior axis may not result in adequate blood pressure until a threshold of compression is reached (see below). The use of infant piglets is favored over young dogs in CPR studies because of their broader chest shape, similar to that of humans. On the other hand, large pigs are less useful because their chest compliance is low, making chest compressions very difficult.

The pharmacokinetics of various anesthetic drugs also differs from species to species. Narcotics, for example, affect many animal species differently than they affect humans. In addition, some animals have higher baseline cerebral blood flow values than humans, and absolute values must be interpreted in that light. On the other hand, the physiology of the myocardial and cerebral vasculature are similar in all vertebrates, so that physiological effects, such as response to adrenergic drugs and endogenous sympathetic stimulation, are comparable. All of these concerns about the comparability of animals and humans apply to the animal studies presented below.

Mechanisms of Blood Flow during CPR

History

For several decades after Kouwenhoven's original description of closed-chest CPR,[1] it generally was assumed that antegrade blood flow during external chest compression resulted from the direct squeezing of the heart between the sternum and spine. If a "cardiac pump" mechanism generates blood flow during external chest compression or "systole," then the ventricles are compressed to a greater extent than the atria in order to generate a ventricular-atrial pressure gradient that will close the atrioventricular valves. Ventricular ejection is accompanied by a reduction in ventricular volume. During chest relaxation or "diastole," ventricular pressure decreases below atrial pressure, leading to opening of the atrioventricular valves and ventricular filling. These cardiac dynamics and flow events mimic a normal cardiac cycle and are operative in open-chest cardiac resuscitation (fig. 1). Several observations of CPR in the 1960s and 1970s were, however, inconsistent with this "cardiac pump" mechanism. Weale and Rothwell-Jackson noted that external chest compression produced equivalent increases in arterial and right atrial pressure.[3] Other clinical observations also raised questions about direct cardiac compression as a sole mechanism of generating blood flow. Rudikoff *et al.* noted that closed-chest CPR failed to generate a measurable blood pressure in some patients with flail sternal segments, a circumstance that should permit direct cardiac compression more readily.[4] Only when the chest was stabilized by external binding could blood pressure be generated. Despite these observations, it was not until the dramatic observation of Criley in 1976[5] that the direct cardiac compression hypothesis was questioned seriously. He reported that several patients who developed ventricular fibrillation during cardiac catheterization could preserve a cardiac output adequate to preserve consciousness by repetitively coughing and phasically elevating intrathoracic pressure. This observation of "cough CPR" focused much subsequent research on whether direct cardiac compression or large fluctuation in intrathoracic pressure was responsible for blood flow during CPR.[5,6]

Thoracic Pump Mechanism

In 1980, Rudikoff *et al.* demonstrated that maneuvers that increased intrathoracic pleural pressure during external chest compression caused increases of intrathoracic vascular pressures. These increased pressures led to increases in carotid blood flow during CPR, suggesting a new mechanism to account for the forward blood flow during closed-chest CPR.[4] This "thoracic pump" hypothesis proposed that blood flow produced by external chest

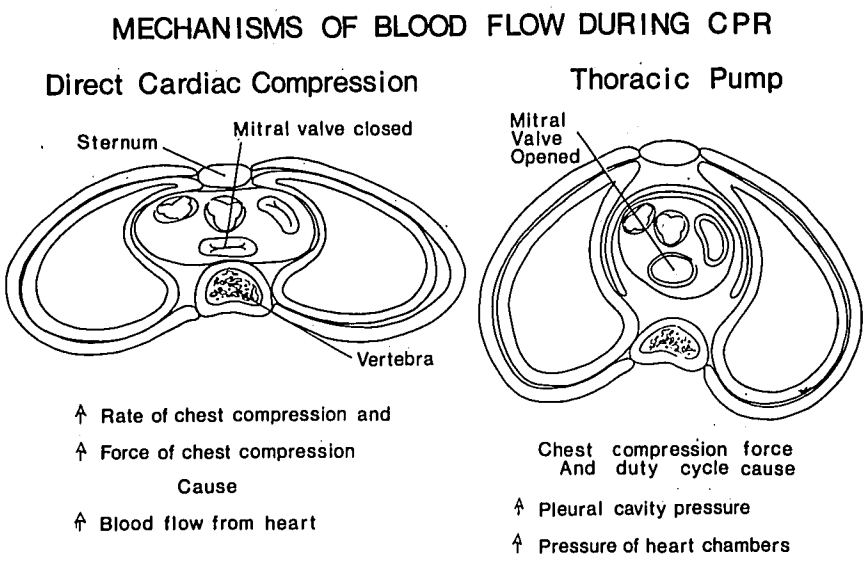

FIG. 1. Possible mechanisms for blood flow during CPR includes direct cardiac compression (left) and the thoracic pump (right). With direct cardiac compression, an increase in chest compression rate causes an increase in blood flow by squeezing the heart between the vertebral column and sternum. With the thoracic pump mechanism, factors that increase pleural pressure cause an increase in pressure within the heart chambers and ultimately an increase in blood flow.

compression could be generated by phasic changes in intrathoracic pressure without direct compression of the heart.[4,7] According to this model, external chest compression produces a generalized elevation of intrathoracic pressure that is transmitted equally to all cardiac chambers and intrathoracic vascular structures. This increase in intravascular pressure is transmitted from the intrathoracic to the extrathoracic arteries. Because of competent venous valves, venous collapse at the thoracic inlet, and a highly compliant extrathoracic venous system, pressure is not transmitted to the extrathoracic veins. Unequal transmission of vascular pressure from the arterial to the venous system provides a gradient for extrathoracic blood flow.[4,7] Implied in the "thoracic pump" mechanism is the antegrade flow of blood through an open mitral valve during chest compression. During "diastole," intrathoracic pressure falls below that of the extrathoracic venous pressure and blood returns to the lungs. The heart plays no active role as a blood pump in this scenario, but serves only as a passive conduit (fig. 1).

Much experimental data supporting the "thoracic pump" mechanism has accumulated over the past several years. Two studies have confirmed a close correlation between the increase in intrapleural pressures and the change in intrathoracic vascular pressures during chest compression.[8,9] Equal pressure increases in all cardiac chambers and thoracic vascular structures have been measured repeatedly during chest compression. Rudikoff *et al.* and Niemann *et al.* have demonstrated the existence of a peripheral vascular gradient sufficient to satisfy the "thoracic pump" theory in the form of a large pressure gradient between the extrathoracic jugular veins and the right atrium during chest compression in dogs and humans.[4,9] Two-dimensional echocardiographic studies during CPR in both dogs[9] and humans[10,11] have shown that, during chest compression, the aortic and mitral valve are open and the left ventricular dimensions are not reduced. Angiographic studies with contrast injection in the pulmonary vein and the left atrium have confirmed that blood flows through the left atrium and the open mitral valve to the left ventricle and aorta during a single chest compression and from the vena cava to the lung during diastole.[9,12] In addition, Niemann *et al.* also demonstrated angiographically that there is a decrease in aortic diameter during chest compression in dogs.[9] If direct cardiac compression were responsible for ejection, an increase rather than a reduction in aortic diameter would be expected. These findings are predicted by the "thoracic pump" theory, in which the heart is a conduit and not a pump.

EVIDENCE FOR CARDIAC PUMP MECHANISM

Most CPR investigators now accept that the "thoracic pump" is responsible for antegrade blood flow with cough CPR, simultaneous compression and ventilation CPR (SCV-CPR), and vest CPR. These are all techniques that involve the diffuse application of energy to the thoracic vasculature (see below). The mechanism of blood flow during modes of CPR delivery that involve the focal application of energy, such as closed-chest manual or mechanical piston CPR, remains controversial.

Babbs *et al.* presented evidence suggesting that direct cardiac compression does occur in small dogs.[13] Weisfeldt and Halperin have commented that direct cardiac compression was noted when very high chest-compression forces were used during some of their experiments, but these forces produced intrathoracic and intraabdominal trauma.[14] Investigators from Duke University Medical School have recently published evidence to support a role

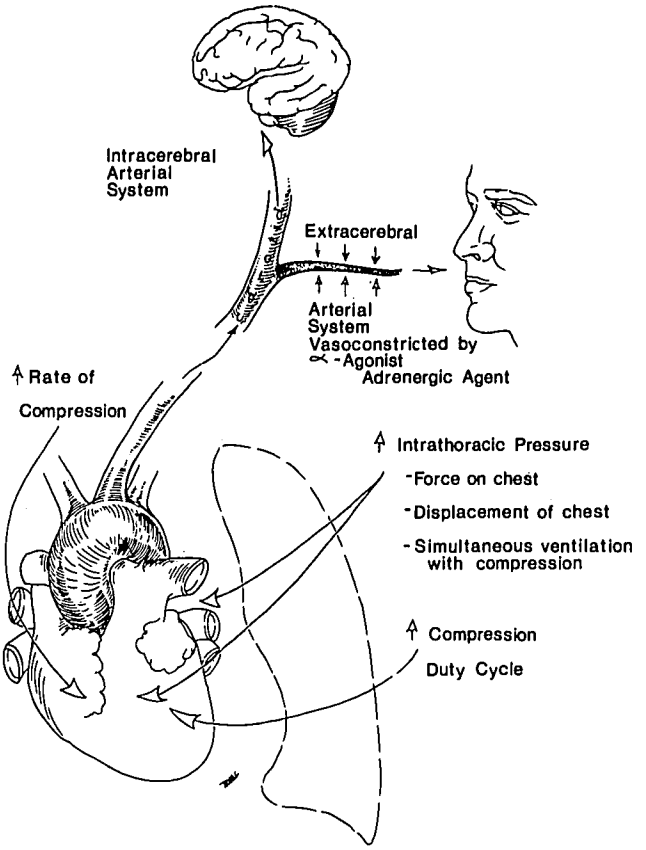

FIG. 2. Factors that increase blood flow from the heart are outlined. An increase in cerebral blood flow is also caused by vasoconstriction of extracerebral blood vessels that shunt blood to the intracerebral vessels.

for direct cardiac compression under certain CPR conditions. They measured ventricular dimensions with chronically implanted ultrasonic transducers during both mechanical and high-impulse manual CPR in dogs. They demonstrated that external chest compressions produced changes in ventricular shape that were characterized by a decreasing diameter of the heart parallel to the force vector of compression and elongation along the other two axes. Although alterations in ventricular shape were demonstrated, changes in ventricular volume which would prove the cardiac pump mechanism were not measured. In addition, these investigators demonstrated that the peak intracardiac and aortic pressures were consistently several times greater than peak intrathoracic pressures measured with a pleural catheter. The changes in ventricular shape and the ventricular-pleural pressure gradient established during chest compression were regarded by these investigators as evidence of a direct cardiac compression mechanism of blood flow during CPR.[15] Further evidence is needed though to clarify whether the cardiac compression mechanism causes blood flow during CPR.

DYNAMICS OF CARDIAC VALVE CLOSURE

Aspects of cardiac valve closure are important in determining which mechanism of blood flow is applicable during CPR. Orderly closing and opening of valves is evidence for the cardiac pump mechanism. If, however, the cardiac valves remain open during external cardiac compression, there is evidence for a "thoracic pump" mechanism of blood flow, since the heart serves only as a passive conduit in this instance. Feneley *et al.* demonstrated with two-dimensional echocardiography in dogs undergoing high-rate manual CPR that the mitral valve closed rapidly and that the left ventricle became deformed with chest compression. Left atrial echocardiographic bubble contrast injections confirmed that antegrade mitral valve flow did not occur during these high-impulse compressions.[16] In contrast, the mitral valve remained open during low-impulse CPR when low-velocity, prolonged compressions were used.[17] Deshmukh *et al.* also provided echocardiographic evidence of a cardiac pump mechanism. During mechanical CPR in arrested minipigs, both two-dimensional and M mode echocardiography revealed closure of the mitral valve during chest compression for the first 5–10 min of CPR. Mitral valve motion diminished with more prolonged CPR only in those animals who could not be resuscitated.[18] In contrast, Werner *et al.* revealed open mitral and tricuspid valves during the entire cycle of CPR. In this case, valve closure is not necessary for forward blood flow and the heart appears to act as a passive conduit for passage of blood.[10]

RATE AND DUTY CYCLE

Further insight into the mechanisms of blood flow during CPR has emerged from studies that have evaluated the hemodynamic changes and the cerebral and myocardial blood flow in response to changes in both the duty cycle and the rate of chest compression during CPR (fig. 2).[19] Duty cycle is defined as the ratio, stated as a percent, of the duration of the compression phase to that of the whole compression-relaxation cycle. For example, at a rate of 30 compressions per minute, a 1-s compression equals a 50% duty cycle.

If blood flow is generated by direct cardiac compression, then the stroke volume will be determined by the force of compression. Prolonging compression and, thus, increase of the duty cycle beyond the time necessary to achieve complete ventricular ejection should have no further effect on stroke volume. Increasing the compression rate will enhance cardiac output, since a fixed volume is ejected with each compression. On the other hand, when blood flow is produced by the "thoracic pump," the mechanism of flow is analogous to a pressure pump. In this instance, blood must be ejected from the large-capacitance thoracic vasculature for systemic blood flow to

occur. Thus, with the thoracic pump mechanism, flow will be enhanced by increasing both the compressive force and the duty cycle, but will not be affected by changes in compression rate over a wide range of compression rates.[14] These predictions assume that venous return does not become a limiting factor during CPR, but no data is available regarding this variable. Mathematical models of the cardiovascular system have confirmed that, if blood flow is due to the thoracic pump mechanism, then it is determined by both the applied force and the compression duration.[20–22] They also show that if direct compression of the heart is a primary determinant of flow, the compression rate and force and not the duration of compression will determine flow.

Halperin *et al.* have examined this question of rate and duty-cycle dependency of blood flow to critical organs during CPR.[19] These investigators measured hemodynamic variables and cerebral and myocardial blood flow in response to varying duty cycles (15–45%) and compression rates (60–150 per minute) in three groups of dogs. One group received closed-chest manual CPR, and a second group received vest CPR—a method of CPR that increases intrathoracic pressure without changing chest dimensions. A third group received CPR by either open-chest cardiac massage or by having the piston of a pneumatic compressor placed directly on the heart after the sternum was removed. In the vest-CPR group, increases in perfusion pressures and flows were produced by increasing the duty cycle from 15 to 45%. Changing the compression rates from 60 to 150 with a constant duty cycle did not increase regional flows. However, in the open-chest cardiac compression group, increasing the compression rate but not the duty cycle increased myocardial perfusion pressures and flows. In addition, the results of the closed-chest manual CPR group were equivalent to those of the vest-CPR group: cerebral and myocardial blood flow and perfusion pressures were increased by prolonging the duty cycle but were unresponsive to rate changes. This study provided further compelling evidence for a thoracic pump mechanism of forward blood flow during manual CPR in dogs. Fitzgerald *et al.* demonstrated that, at a fixed duty cycle in dogs with closed-chest manual CPR, cardiac output was unchanged with compression rates between 60 and 120. At a constant compression rate of 60 per minute, cardiac output was maximized with a duty cycle of 40% but deteriorated dramatically with either extremely short or long duty cycles.[23]

The effect on cardiac output and myocardial blood flow of varying compression rates was also examined by Maier *et al.*[15] Using high-impulse manual chest compressions in a dog CPR model, these investigators demonstrated that a stepwise increase in compression rate from 60 per minute increased cardiac output but not stroke volume. At 100 and 150 per minute, cardiac output was enhanced by 150 and 230%, respectively. Coronary blood flow was not augmented by increasing compression rate. The increase in cardiac output in this study could also be attributed to a concomitant increase in duty cycle. The duty cycle can increase when the compression rate increases if the absolute time of compression remains the same at a higher rate. If this were the case, the study would be supportive of the thoracic pump and not the cardiac pump mechanism of antegrade blood flow.

The efficacy of the high-impulse rapid-compression CPR technique is supported by the work of Feneley *et al.*[24] Dogs subjected to a higher chest-compression rate (120/minute) were resuscitated more successfully to a life-sustaining rhythm than those receiving slower chest compressions (60/minute) (12 of 13 *versus* 2 of 13 animals). In addition, the fast-compression-rate group of animals had a better 24-h survival rate (62% *versus* 15% for the slower-rate group) and less neurologic damage. The better survival in the fast-compression-rate group correlated with a higher aortic diastolic pressure and myocardial perfusion pressure. In this study, an attempt was made to achieve the same duty cycle in both groups. Duty cycle was not directly measured but, rather, was calculated from an aortic pressure tracing, which could lead to a false assumption if peripheral vasoconstriction with prolonged arterial runoff exists. In this case, duty cycle might be overestimated by measuring the timing of the aortic pressure tracing.

Halperin's study discussed above supported the conclusions of a CPR study in humans by Taylor *et al.* in 1973.[25] These investigators measured common carotid blood flow by ultrasonic Doppler flowmeter during mechanical, closed-chest CPR in humans performed by a pneumatic piston chest-compression device. Duty cycle and force of compressions were controlled by a computer. The study demonstrated that the effectiveness of chest compressions depended on duty cycle rather than on rate. At a constant rate of 60 compressions per minute, flows progressively increased as duty cycle was increased from 30 to 60%. Changing the compression rate from 40 to 80 per minute with a duty cycle of 60% did not enhance these flows.

Thus, it appears from the experimental animal data and more limited human data that both the "thoracic pump" and "cardiac pump" mechanisms can effectively generate blood flow during closed-chest CPR. Discrepancies among the results of various studies may be attributed to differences in CPR models and compression techniques. These differences may involve issues of chest compliance and geometry, maturity of different animal species,[26,27] or chest compression techniques. The differences in techniques may include magnitude of sternal displacement, compression force and momentum of chest compression, compression rate, or duty cycle.

The 1986 American Heart Association guidelines for CPR and Emergency Cardiac Care have increased the recommended rate of chest compression rate from 60 to 100.[2] This change represents a compromise between advocates of the "thoracic pump" mechanism and those who support the mechanism of blood flow by direct cardiac compression.[14] On the basis of their canine studies, Maier *et al.* recommended an increase in the chest compression rate to 120 per minute.[15] Proponents of the "thoracic pump" mechanism have suggested that more emphasis be placed on the duration of compression and a chest compression rate be chosen that can most readily achieve a duty cycle of 50%. At a rate of 60 per minute, a pause between chest compressions is required to achieve a 50% duty cycle. This is tiring and difficult to accomplish for the rescuer. A faster rate of approximately 100 per minute more readily permits the resuscitator to achieve a 50% duty cycle and satisfies those who recommend faster chest compressions.[14]

Newer CPR Techniques

Simultaneous Compression-Ventilation CPR

An understanding of the mechanisms of blood flow during CPR has led to research and development of new CPR techniques. Some of these new CPR modes require sophisticated mechanical equipment and intubation of the patients' trachea and are therefore not suitable for the initiation of basic CPR. Other techniques are relatively simple but clinical evaluation has not proved their superior efficacy.

If phasic elevations of intrathoracic pressure can generate blood flow during CPR then, for the same sternal displacement, manipulations that augment intrapleural and intrathoracic vascular pressures should increase antegrade blood flow during CPR. Several innovative mechanical techniques have been investigated over the past several years in both the research laboratory and in clinical trials. None of these newer techniques have as yet been approved by the American Heart Association for use during CPR.

Simultaneous compression and ventilation CPR (SCV-CPR) was a logical development based on the thoracic pump mechanism of blood flow during CPR. Chandra *et al.* demonstrated that the simultaneous application of external chest compression and ventilation at high airway pressure (80–100 mmHg) is a technique that increases intrathoracic pressure when compared with conventional closed-chest CPR.[28] This technique has produced greater increases of aortic blood pressure, cardiac output, and carotid blood flow in both human[28] and animal [29] CPR studies than conventional CPR techniques. Subsequent studies have confirmed the efficacy of this technique in enhancing cardiac output and regional cerebral and coronary blood flow in canine models of CPR.[30,31] However, in infant piglets[32] and small dogs,[27] SCV-CPR does not surpass standard CPR in raising intrathoracic pressure, systemic blood pressure, or critical organ perfusion. Perhaps the particular chest geometry and compliance in these small animals allow high intrathoracic pressure to be achieved by standard CPR.[26]

Vest CPR

CPR performed by the phasic inflation at high pressure by 280–350 cm H_2O of a circumferential chest vest has been investigated in the laboratory as a mode of CPR that does not need complex simultaneous ventilation devices.[19,31,33] Vest CPR is a method of increasing intrathoracic pressure by phasically inflating a bladder around an animal's chest, in order to increase intrathoracic pressure, without significantly changing the dimensions of the chest. Clinical trials with this technique are in progress. The advantages of vest CPR over standard CPR are twofold. Intrathoracic pressure is increased by a uniform, circumferential decrease in chest dimensions rather than by the focal distortion of a relatively small area of the chest. Trauma to the chest wall and viscera, a frequent complication of standard CPR, might also be obviated. In dogs, vest CPR at very high inflating vest pressures (greater than 300 mmHg) generated cerebral and myocardial blood flows equal to prearrest values. However, these animals frequently suffered severe myocardial and pulmonary contusions. At lower inflating pressures (280 mmHg), cerebral blood flow was maintained at prearrest values while myocardial flows were reduced by 50%. No visceral trauma was produced in these groups of animals.[33]

Abdominal Compression

Abdominal binding or continuous abdominal pressure during conventional or SCV-CPR has increased aortic pressure and carotid blood flow in both human[34] and animal[35] studies. These maneuvers increase intrathoracic pressure during chest compression by limiting the caudad movement of the diaphragm and preventing the dissipation of the intrathoracic pressure that is generated.[35] In addition, abdominal binding may also redirect blood flow from below the diaphragm, resulting in an increase in central blood volume. The increase in systolic and diastolic aortic pressures generated by abdominal binding has not been shown to increase myocardial perfusion pressure.[36] There is an increase in right atrial pressure that exceeds the increase in aortic diastolic pressure and subsequently decreases myocardial perfusion pressure. In this study, left atrial pressure is not measured and so right atrial pressure is used as the downstream pressure. Subsequent studies also have confirmed that abdominal bind-

ing in dogs fails to increase regional myocardial blood flow when compared with conventional CPR alone.[35] When applied during SCV-CPR, abdominal binding decreases the cerebral perfusion pressure. This occurs because of transmission of intrathoracic pressure to the intracranial vault, resulting in increased intracranial pressure. The increase in downstream pressure more than offsets the increase in upstream carotid pressure, resulting in a lowered cerebral perfusion pressure.[30]

The hemodynamic effects of military antishock trousers (MAST) during closed chest CPR has been found to mimic the vascular effects of abdominal binding.[37,38] Aortic systolic and diastolic pressures were greater than with standard CPR alone. Right atrial and intracranial pressures were also increased, however, so that myocardial and cerebral perfusion pressures did not increase. Several clinical studies have also demonstrated that MAST-augmented CPR does not increase the survival rate from cardiac arrest.[39,40]

Interposed abdominal counterpulsation CPR (IAC-CPR) consists of the application of interposed abdominal compression either manually or by phasic inflation of a circumferential vest around the abdomen, during the relaxation phase of the chest compression cycle of conventional CPR.[41] No compression is applied to the abdomen during chest compression. This technique involves the participation of at least two resuscitators. Babbs *et al.* has suggested that IAC-CPR be considered as an example of a third mechanism for blood flow generation during CPR, the "abdominal pump."[42] This abdominal pump resembles an intra-aortic balloon pump. Abdominal counterpulsation increases venous return and also compresses the abdominal aorta to produce retrograde aortic flow, closing the aortic valve and enhancing aortic diastolic pressure. Since the abdominal compression partially sustains the increase in intrathoracic pressure of the chest compression phase, an increase in the effective duty cycle may be an additional physiologic effect of IAC-CPR.[43] The efficacy of this CPR mode has been demonstrated by Babbs *et al.* in an electrical model of the circulation.[20] In animal experiments, cardiac output, systemic oxygen uptake, and both cerebral blood flow and myocardial blood flow are substantially enhanced by this technique when compared with standard CPR.[44,45] Walker *et al.* demonstrated a 450% increase in cerebral cortical flow with IAC-CPR.[46] Voorhees *et al.* demonstrated that interposed abdominal counterpulsation and epinephrine during CPR can produce cerebral blood flow values during CPR that are indistinguishable from control values.[45] Clinical studies by Berryman *et al.*[47] and Howard *et al.*[48] demonstrated an increase in mean arterial pressure and myocardial perfusion pressure during IAC-CPR when compared with standard CPR. There was, however, no improvement in long-term clinical outcome. A number of laboratory[45,49] and clinical studies[47,50] have failed to demonstrate an increase in the frequency of complications, including hepatic laceration or esophageal regurgitation, with IAC-CPR compared to standard CPR. The technique does have potential weaknesses, however. It is difficult to perform because of the need for an extra rescuer. Although studies have not shown an increase in the rate of complications due to abdominal trauma, larger series may show this to be a problem. As of yet, no long-term studies have shown an increased survival using this method, so further work needs to be done before the technique is incorporated into standard CPR practice.

These newer techniques of CPR have not yet been accepted into clinical practice because of some of the limitations already alluded to. The use of SCV-CPR is difficult in the clinical arena because of the need for intubation of the patient's trachea and for delivery of high airway pressure. It has been more successful in dog studies in successfully resuscitating the heart than conventional closed-chest CPR. On the other hand, human studies that definitely prove the efficacy of the technique have not been performed. The anatomical and size differences between dogs and humans may also play a critical role in the utility of this technique. The chest shape of the dog may be sufficiently different from the human chest to allow different mechanisms to play a role in the generation of blood flow during CPR. SCV-CPR would have no advantage over conventional closed-chest CPR if direct cardiac compression is important in humans.

Vest CPR also depends on the use of sophisticated equipment, making it difficult and cumbersome in the field. At this juncture, its use is theoretical and allows us to differentiate various mechanisms of blood flow during CPR in the laboratory setting. Abdominal compressions, either in a continuous or interposed fashion, have had mixed results. Even though aortic pressure is increased by these methods, perfusion pressure of vital organs is not, so ultimate outcome may not be favored.

It is possible then, if clinical studies in humans substantiate some of the animal data, that these techniques could be utilized in order to maximize regional blood flow during CPR. With the use of microprocessor systems to control inflation of abdominal and chest vests and with the increased sophistication of hospital and field personnel, techniques such as SCV-CPR might be used both in and out of the hospital.

Open-chest Cardiac Massage

The use of open-chest cardiac massage has been replaced primarily by closed-chest CPR since the early 1960s. Nevertheless, there continue to be a number of indications for its use and some physiologic studies have shown it to be superior to closed-chest CPR in generating blood flow.

Physiology—Generation of Blood Flow. The generation of blood flow with open-chest CPR is better than with closed-chest CPR in most studies. Weiser *et al.* found cardiac output to be three times greater in dogs treated with open-chest CPR than in those having closed-chest CPR.[51] In addition, they found significant improvement in aortic mean pressure with open-chest CPR.[51] Bircher *et al.* also showed improvement in hemodynamic variables and coronary and cerebral perfusion pressures when open-chest CPR was instituted in dogs following a trial of closed-chest CPR. In addition, EEG activity and pupillary findings were improved with open-chest CPR.[52] Sanders *et al.* showed that open-chest CPR, when performed after 15 min of closed-chest CPR, significantly improved coronary perfusion pressure and the rate of successful resuscitation.[53] After 20–25-min periods of closed-chest CPR in a separate experiment, hemodynamic variables were improved. The lower coronary and cerebral perfusion pressure during closed-chest CPR compared to open-chest CPR is due to generation of higher right atrial pressure (used to measure coronary perfusion pressure) and intracranial pressure.[54]

Del Guercio *et al.* compared open-chest and closed-chest CPR in a human study. They found that the stroke index and cardiac index were higher and the mean circulation time shorter when open-chest CPR was performed.[55]

Indications. The American Heart Association's Standards and Guidelines for CPR and ECC propose several indications for open-chest CPR. These include cardiac arrest secondary to penetrating chest trauma, anatomic chest-wall abnormalities that make closed-chest CPR impossible, cardiac tamponade, cardiac arrest in the face of critical aortic stenosis, cardiac arrest during surgery in which the chest is already opened, crushed chest injury, cardiac arrest secondary to hypothermia, cardiac arrest secondary to a ruptured aortic aneurysm when cardiopulmonary bypass facilities are immediately available, and failure of adequately applied closed-chest CPR.[2]

The last point causes the most controversy. Kern *et al.* discussed this issue and brought up a number of controversial areas including the definition of ineffective closed-chest CPR and the timing of instituting open-chest CPR when closed-chest CPR has failed.[56] They performed experiments to determine if the time of initiation of open-chest CPR following closed-chest CPR influences the success of resuscitation. The study demonstrated that open-chest CPR may improve initial resuscitation success when applied early.[54] It appears that open-chest CPR is more effective in improving the rate of successful resuscitation if efforts at ineffective closed-chest compressions are not continued for very long periods.[56]

Thus, there is evidence that open-chest CPR is superior to closed-chest CPR in improving blood pressure and blood flow. Nevertheless, open-chest CPR is not a means of CPR that can be employed by lay people or by most physicians. There are firm indications for open-chest CPR as published by the American Heart Association but controversy continues regarding its use in patients with nontraumatic cardiac arrest. Future studies should be aimed at determining the timing of instituting open-chest CPR when closed-chest CPR is unsuccessful at restoring spontaneous circulation.

Position of Chest Compression in Children

Another change in the mechanical delivery of closed-chest CPR, recommended by the American Heart Association Standards and Guidelines for CPR and ECC,[2] is the sternal landmark position for chest compression in infants. Previously, the position of the heart in infants was thought to be more cephalad than in adults, possibly because of lung deflation in the postmortem period,[57] so the recommendation was that chest compressions be applied over the midsternum during closed-chest CPR. Chest compressions over this location might also reduce the possibility of abdominal visceral injury. Recent radiological studies by Orlowski[58] and Phillips *et al.*[59] demonstrated that the heart lies under the lower third of the sternum in infants and children.

In the infant, the recommended point of compression is one finger breadth below the intersection of the intermammary line and the sternum. In the child, the heel of the compressing hand is placed one finger breadth cephalad to the junction of rib cage and the sternum.[2]

Differences in Chest Geometry and Compliance

Distinct differences are found in chest compliance and geometry of the thoracic cavity when infants, older children, and adults are compared. These differences in chest properties may alter the relationship between the degree of sternal displacement and intrathoracic and intravascular pressures generated by chest compression, or may determine whether or not there is direct compression of the heart. For example, in the infant with its very compliant chest, a certain amount of sternal displacement (as a percent of the total anteroposterior chest diameter) might more readily allow for direct compression of the heart or an augmentation of intrathoracic pressure during conventional CPR.

Babbs *et al.* demonstrated that various modes of CPR affect cardiac output differently when they are applied to animals of different sizes. In large dogs, which have an anteroposterior diameter greater than that of adult humans, SCV-CPR generated a higher cardiac output than conventional CPR modalities.[13] In smaller dogs, conventional and SCV-CPR generated equal levels of cardiac output.[13,60] The authors suggested that, in the larger an-

imals, external chest compression probably generates blood flow by the thoracic pump mechanism, whereas in smaller dogs with more compliant chests either cardiac output was the result of direct cardiac compression or equal and high levels of intrathoracic pressure were generated by both techniques.

Our group of investigators hypothesized that differences in chest geometry between infant and adult animals accounted for the efficacy of standard CPR in the infant animal model and its inability to generate adequate cardiac output in adult animals.[61] We attempted to delineate alterations in chest geometry occurring in 2-week-old, 1-month-old, and 3-month-old piglets during conventional CPR and to correlate the different patterns of alteration with the amount of intrathoracic vascular pressure generated. We found that alteration in chest geometry during CPR did depend on the age of the animal.[61] The magnitude of the intrathoracic vascular pressure generated during chest compression depended on the chest stiffness of the animals in each age group and so was related to changes in chest geometry. We proposed a thoracic index to quantify the relationship between chest geometry and response to CPR. If the thorax is conceived as an elliptical cylinder, the thoracic index describes the ratio of the anteroposterior to lateral chest diameter. With a thoracic index less than one, ejection occurs with any amount of compression and the displacement of the chest needed for flow does not need to reach a threshold level. If the thoracic index is greater than one, as in the dog, there is a threshold of displacement of the chest before which ejection of blood does not take place.

Despite high compression forces, negligible fractional anteroposterior displacement could be obtained in the older (3-month-old) piglets. The geometric threshold for ejection, in this case, was not exceeded, and positive intrathoracic pressure was not generated. In contrast, younger animals, with their more compliant chests, develop significant permanent chest deformity, and so, just after beginning CPR, develop a thoracic index less than unity. As a result, positive ejection of blood from the thoracic cavity is easily obtained, resulting in adequate cerebral and myocardial blood flow. As chest deformity develops, the thoracic index decreases, and a greater ejection of blood would be predicted for a given pulsatile chest displacement. In animals with a thoracic index of 1.1, as seen in younger piglets, moderate chest deformity would overcome the displacement threshold and result in blood flow.[61] We previously showed that, within minutes of instituting conventional CPR with anterior chest compressions, a 20% deformity of the initial anteroposterior diameter of the infant piglets' chest developed, leading to superior cerebral and myocardial blood flow.[26]

In the human, the thoracic index is less than one in all age groups. The newborn has a thoracic index of .75, decreasing to .64 in the older infant, .60 in the 6–8-year-old, and .59 to .64 in the adult.[38] These indices may reveal the reason for the difference in efficacy of CPR between animal studies and those in humans. With a thoracic index less than one, conventional CPR would be expected to generate higher amounts of blood flow for a given pulsatile displacement of the chest. In infants, whose chest compliance is high enough to allow for adequate displacement of the chest, CPR would be expected to be especially effective, and there would be no threshold for displacement, according to the model. Thus, it is possible that CPR in humans is more efficacious in infants than in older children or adults due to these concerns of size and compliance. Clinical human studies might help in determining what parameters of chest displacement or type of CPR (*e.g.*, conventional or SCV-CPR) should be used for the particular age group in question. In adults, whose chest compliance is lower than that of children, the generation of higher intrathoracic pressure might be beneficial.

For animal studies of CPR, a model should be chosen that is as similar as possible to the human in terms of chest size and compliance, *i.e.*, it should have a thoracic index less than one and have a similar compliance. Thus, we have chosen to use infant piglets, which have a thoracic index of nearly one. For adult animal preparations, dogs have been used because they have a similar chest compliance, although their thoracic index is greater than that of humans. In addition, to choose an appropriate model, compliance and thoracic index must be taken account of in interpreting animal studies. Sufficient force of chest compression needs to be used to overcome the threshold for ejection of blood in animals with chests having a thoracic index greater than one. When studying mechanism of flow, the particular chest compliance and displacement of the chest wall should be recorded in order to determine their similarity to those of humans.

Adrenergic Drug Effects

Shortly after the initial descriptions of closed-chest CPR were published, the use of adrenergic agonists during resuscitation was described.[62] In 1963, Redding and Pearson showed in a dog model of CPR that earlier administration of epinephrine during an arrest improved the success rate of resuscitation.[62] In a later study, they demonstrated that an increase in the aortic diastolic pressure was responsible for this improved outcome.[63] They postulated that vasopressors such as epinephrine were of value because they improved peripheral vascular tone.

Yakaitis *et al.* investigated the relative importance of alpha- and beta-adrenergic agonist action of epinephrine during resuscitation.[64] Only 27% of dogs that received both alpha-receptor blocking agents and beta-adrenergic agonists, such as isoproterenol, were resuscitated suc-

TABLE 2. Adrenergic Agonists

Alpha Adrenergic Effects
Advantages
Vasoconstricts peripheral vascular beds
Increases diastolic pressure; increases coronary blood flow
Vasoconstricts extracerebral carotid blood vessels; increases intracerebral blood flow
Drugs
Epinephrine
Phenylephrine
Beta Adrenergic Effects
Advantages
Increases vigor of ventricular fibrillation
Positive inotrope
Disadvantages
Increases oxygen demand of organs such as heart and brain
Increases arrhythmias following resuscitation
Increases heart rate following resuscitation causing an increase in oxygen demand
Drugs
Epinephrine

cessfully. On the other hand, all the dogs that received alpha-adrenergic agonist agents and beta-adrenergic antagonists were resuscitated successfully. This data suggested that the alpha-adrenergic action of epinephrine was responsible for its beneficial effects during resuscitation.[64]

In more recent studies, using either conventional or SCV-CPR, Michael *et al.* demonstrated that the effects of epinephrine during CPR were mediated by selective vasoconstriction in noncerebral and nonmyocardial vascular beds. When epinephrine was infused, higher aortic systolic and diastolic pressures were maintained with no alteration of right atrial (when used to determine coronary perfusion pressure) or intracranial pressures, resulting in higher vascular perfusion pressures for the heart and brain.[65] Similar results have been observed in an infant swine model of CPR.[26] When epinephrine was infused, peripheral organ blood flow to the jejunum and kidney was decreased despite high aortic pressures. This data supports the concept that epinephrine enhances cerebral and myocardial perfusion by selective vasoconstriction of peripheral vascular beds, which raises perfusion pressure for the brain and heart (Table 2).[26,65]

CORONARY BLOOD FLOW

The contractile state of the myocardium is enhanced by the beta-adrenergic effects of epinephrine. During resuscitation, this beta-agonist action is thought to result in the stimulation of spontaneous myocardial contractions and an increase in the intensity of ventricular fibrillation. Contrary to this opinion, Livesay hypothesized that the inotropic effects of beta-adrenergic agonist drugs might actually be deleterious to the fibrillating heart.[66] During fibrillation, epinephrine may increase the intramyocardial wall pressure and hence the downstream pressure for myocardial perfusion. The increase in downstream pressure would decrease coronary perfusion pressure and result in a decreased subendocardial blood flow. Beta-adrenergic stimulation might also increase the myocardial oxygen demand superimposed on the decrease in blood flow. In normally beating hearts, subendocardial blood flow occurs almost entirely during diastole. Ventricular fibrillation has been shown to simulate a period of sustained systole. Thus, during ventricular fibrillation intramyocardial wall pressure is higher, causing a decrease in myocardial perfusion pressure and blood flow. This combination of increasing oxygen demand and decreasing oxygen supply may cause further damage to an already ischemic heart.

Epinephrine has been the drug of choice for resuscitation. The administration of a pure alpha-adrenergic receptor agonist, such as phenylephrine or methoxamine, might be advantageous during CPR. These drugs, like epinephrine, cause peripheral vasoconstriction during CPR, leading to an increase in aortic diastolic pressure. However, they may not cause an increase in the oxygen demand of the heart, and thus there may be a more favorable oxygen supply-*versus*-demand ratio in the ischemic heart. Successful resuscitation with alpha-adrenergic agonist agents has been shown in animal studies.[62]

Some studies have shown that a pure alpha-adrenergic agonist does maintain myocardial blood flow during CPR.[64] In a recent study, we found that high values of arterial pressure can be sustained with a continuous intravenous infusion of phenylephrine. Moreover, the high level of myocardial perfusion and low level of abdominal visceral and noncerebral cephalic perfusion were equivalent in the phenylephrine and epinephrine animal groups. The increased myocardial perfusion pressure created by infusion of either phenylephrine or epinephrine led to a 75% success rate for defibrillation with either drug.[67] This agrees with earlier studies.[63,64]

However, several studies have found that myocardial blood flow tended to be lower during CPR in animals given a pure alpha-adrenergic agonist rather than epinephrine. The arterial pressure achieved with the doses of drug in these studies was lower and may have contributed to the decrease in myocardial blood flow.[68–70] Thus, the literature reveals conflicting reports on the relative merits of a pure alpha-adrenergic agonist compared to epinephrine in terms of generating coronary blood flow during CPR. Clearly, these effects on flow and metabolism still need investigation.

CEREBRAL BLOOD FLOW

The effects of alpha-adrenergic agonists on the cerebral vasculature during CPR are similar to its effects on myo-

cardial blood flow. Epinephrine has been found to produce selective vasoconstriction in noncerebral peripheral vascular beds (fig. 2).[65,68,71] Epinephrine infusion maintained higher aortic systolic and diastolic pressures for perfusing the head and brain without markedly altering right atrial or intracranial pressure.[65] As described previously, in an infant piglet model of CPR, cerebral blood flow was maintained with an epinephrine infusion for 35 min of CPR.[26] Another study compared epinephrine and phenylephrine in generating cerebral blood flow during CPR. In both drug groups, cerebral blood flow was maintained at prearrest levels for 20 min of CPR. In addition, cerebral oxygen uptake was sustained in both drug groups for that period without reaching maximal oxygen extraction, implying that cerebral blood flow was higher than is necessary to maintain adequate cerebral metabolism.[72]

These results differ from other studies that showed superior cerebral blood flow with epinephrine compared to alpha-adrenergic agonists, phenylephrine, or methoxamine during conventional CPR in swine.[69,70,73] A longer ischemia time of 10 min was allowed in those studies before commencement of CPR. The lower blood flow they achieved with either 0.1 mg/kg[74] or 1 mg/kg[69] of phenylephrine compared with 0.2 mg/kg of epinephrine[69,74] is probably due to the lower aortic pressure achieved with these doses of phenylephrine. When a higher dose (10 mg) of phenylephrine was used,[69] aortic pressure and cerebral blood flow were similar to that observed with the use of epinephrine. The potency of the higher dose of phenylephrine may be equal to that of the lower dose of epinephrine used in this study.

Cerebral oxygen demand may be stimulated by central beta adrenoceptors if sufficient amounts of epinephrine cross the blood–brain barrier.[75,76] This crossing can occur if there is mechanical disruption of the barrier or if enzymatic barriers to vasopressors are overwhelmed in the presence of tissue hypoxia.[77,78] The blood–brain barrier could be disrupted during the large fluctuation of cerebral venous and arterial pressures during chest compression or by the surge of arterial pressure that may occur in a maximally dilated vascular bed after ventricular defibrillation.[79] Stimulation of oxygen demand at a time when blood flow is limited during CPR could affect cerebral recovery adversely. A recent study contrasting the use of epinephrine and phenylephrine administered 9 min after fibrillation failed to detect differences in neurological deficits 24 h later.[80]

Blood–Brain Barrier

With blood–brain barrier disruption, an alpha-adrenergic agonist may cause vasoconstriction, resulting in lowering of cerebral blood flow. Epinephrine may vasoconstrict or vasodilate cerebral vessels depending on the balance between alpha- and beta-adrenergic effects.[81] In our recent study, in which cerebral ischemia was very brief, we found no evidence that epinephrine had a different effect on cerebral blood flow or cerebral oxygen uptake than phenylephrine.[67] It is possible that, with more prolonged ischemia prior to the onset of CPR, the blood–brain barrier is more prone to disruption during CPR and significant amounts of high circulating adrenergic agonists will gain access to the brain.

Dosage

Recent investigations have attempted to determine the optimal dose of vasopressor needed during CPR. In an infant piglet model of CPR, epinephrine was administered in increasing doses of 0, 1, 10, and 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ by constant infusion during conventional CPR. With 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion, epinephrine caused higher cerebral perfusion pressure and blood flow during CPR than before arrest. Increasing the epinephrine infusion dose to 10 or to 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ produced no further increase in cerebral blood flow but maintained flow for a more prolonged period of CPR. Increasing the dose of epinephrine over the 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion did not increase cerebral oxygen uptake or cerebral oxygen extraction. Myocardial blood flow increased when at least 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ was infused. Epinephrine infused at 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ produced no further increase in myocardial blood flow.[82] In an adult swine model of CPR, increasing doses of epinephrine were given, ranging from 20 $\mu g/kg$ to 2000 $\mu g/kg$ and a beneficial effect on cerebral and myocardial blood flow occurred when the dose was at least 200 $\mu g/kg$.[73] The drug was given as a single bolus through a peripheral iv following a 10-min cardiopulmonary arrest and 3 min of CPR.

These studies suggest that the dose of epinephrine needed to optimize blood flow to vital organs such as brain and heart may be greater than doses recommended in current standards. The dose of epinephrine currently advocated by the American Heart Association in the Standards & Guidelines of CPR & ECC is 10 $\mu g/kg$ (.01 mg/kg) administered every 5 min.[2] The use of much higher doses of epinephrine, possibly administered by constant infusion, may be warranted in the CPR setting, since increases in regional blood flow have been seen with larger doses.

Sodium Bicarbonate

Sodium bicarbonate has been a mainstay of drug therapy during CPR until the most recent American Heart Association guidelines.[2] The guidelines for bicarbonate use changed because of the paucity of data supporting improved outcome with its use following cardiac arrest.

Moreover, there are data indicating that bicarbonate may have a number of adverse effects.

Sodium bicarbonate is indicated for significant metabolic acidosis occurring during cardiac arrest and CPR. The metabolic acidosis seen during circulatory arrest is due to the accumulation of lactic acid and other metabolites formed during anaerobic metabolism associated with this low perfusion state.

An exacerbation of central venous acidosis during CPR has been documented in both animal[83] and human studies.[84] Weil *et al.* described an arteriovenous gradient for *p*H and p_{CO_2} during CPR, with a predominant respiratory acidemia on the venous side of the circulation. They theorized that the arterial alkalemia was due to the high ratio of pulmonary ventilation compared with perfusion during the low flow states occurring during CPR.[83] Venous blood gases reflect the increased carbon dioxide load that develops during CPR when pulmonary and systemic blood flow are decreased. Weil's studies also assume a situation in which there is low pulmonary flow shunt so that carbon dioxide is excreted efficiently.

In these studies, no attempt was made to measure lactic acid or other metabolites during CPR. These measurements would be necessary to clarify further the acid-base status during CPR. In addition, in Weil's studies, very low intrathoracic vascular pressures were generated during CPR.[83] Cardiac output and pulmonary blood flow could be enhanced during CPR by the use of vasopressors or other CPR modes discussed above. With an increase in pulmonary blood flow, carbon dioxide excretion might be augmented, resulting in a decrease in mixed venous P_{CO_2}.

The metabolic acidosis that develops during a cardiac arrest and CPR may have widespread detrimental effects. Systemic acidosis compromises myocardial function by depressing diastolic depolarization, spontaneous cardiac activity, electrical threshold for ventricular fibrillation, the inotropic state of the myocardium, and cardiac responsiveness to catecholamines. More severe myocardial depression is seen with respiratory acidosis than with metabolic acidosis.[85,86] Intracellular acidosis is due to the rapid entry of carbon dioxide into the cells with a slower egress from the cells of bicarbonate and hydrogen ions, resulting in a lower intracellular *p*H.[85,87] These effects may also be seen in the brain, where carbon dioxide formed by the dissociation of bicarbonate rapidly enters neurons while there is a slower exit of hydrogen ions from the cells. If this phenomenon occurs, it may lead to cerebrospinal fluid acidemia during sodium bicarbonate therapy,[88] which may cause CNS dysfunction.

Arterial systemic acidosis also affects the peripheral circulation, causing a decrease in systemic vascular resistance. The responsiveness of the peripheral circulation to both alpha- and beta-adrenergic stimulation is decreased with acidosis, although, with larger doses of adrenergic agents, this effect may be overcome.[89,90] For instance, isoproterenol increased cardiac output in one study in the face of severe respiratory acidosis.[91]

Lactic acidosis in cardiac arrest and CPR is thought to have important pathophysiologic consequences. The arguments for and against bicarbonate therapy in the setting of lactic acidosis were discussed recently.[92,93] Stacpoole argues that the use of sodium bicarbonate is no longer warranted given the paucity of data supporting its effectiveness in clinical situations.[92] Guerci *et al.* did not find that bicarbonate had a more beneficial effect in defibrillating dogs than saline.[94] Other data indicate that the use of bicarbonate not only fails to confer benefit, but may actually be deleterious in the treatment of lactic acidosis.[95] The mortality rate in diabetic dogs made acidotic by phenformin was no different in a bicarbonate-treated group than in a control group.[96] These models are arguably not very applicable to clinical CPR situations. Narins and Cohen argue that bicarbonate treatment is a temporizing measure that increases a potentially lethal *p*H until the underlying cause of the acidosis is treated and adequate circulation is restored.[93]

The paradox of the production of intracellular and central nervous system acidosis seen with the use of sodium bicarbonate is cited by some as an important contraindication to bicarbonate therapy.[92] However, this phenomenon may not be clinically relevant. Recently, a group of investigators demonstrated that administering sodium bicarbonate to neonatal rabbits recovering from hypoxic lactic acidosis increased arterial *p*H without producing a paradoxical intracellular acidosis in the brain.[97] Another argument against the use of alkali therapy during CPR is based on its effect on the oxygen dissociation curve. Some argue that when the curve is shifted leftward, oxygen delivery to the tissues is further decreased at a time when it is already low. The clinincal relevance of this phenomenon is undetermined. In addition, the increased serum osmolality and hypernatremia that can be produced by bicarbonate administration may be deleterious in the CPR setting.

In conclusion, the use of bicarbonate for treating acidosis during cardiac arrest and CPR is still vigorously debated. All investigators agree that the most critical step in treating lactic acidosis is the identification and correction of the underlying cause. Bicarbonate administration in the CPR setting may be warranted in patients who have had a long period of cardiac arrest or who have severe acidosis and in whom an adequate airway and ventilation have been established prior to bicarbonate administration. Thus, its efficacy in clinically relevant situations needs to be defined further.

Glucose

Administering glucose during CPR is controversial at this time because of the potential detrimental effects on the brain of hyperglycemia during ischemia. Over the past decade, advances have been made in the understanding of many facets of the pathophysiology during cerebral ischemia. The association of hyperglycemia with aggravation of cerebral ischemic damage was initially reported by Myers *et al.*[98] and confirmed subsequently by other investigators in animal models of both focal and global ischemia.[99–102] These studies have all demonstrated that when hyperglycemia is produced prior to a cerebral ischemic event, the neurologic outcome is worse than in normoglycemic animal controls.

The mechanism of this worsened outcome is felt to be an increase in lactic acid in the brain. Lactic acid is produced during ischemia because of anaerobic metabolism, which is increased in a hyperglycemic milieu. The resultant acidosis aggravates neuronal injury.[103] In humans, there is evidence that clinical outcome following an episode of cerebral ischemia is worsened by hyperglycemia. Pulsinelli *et al.* found that patients with hyperglycemia had a poorer neurologic outcome after ischemic strokes.[104]

In the clinical context of cardiac arrest and advanced cardiac life support, a glucose-containing fluid is routinely administered for drug administration. A bolus of a 50% glucose solution is frequently administered to the unconscious patient to treat possible hypoglycemia as a cause of this altered state. However, hyperglycemia produced by the administration of glucose may worsen the cerebral ischemic damage already produced by the cardiac arrest and subsequent reperfusion with low cerebral blood flow. D'Alecy *et al.*[105] demonstrated in a canine model of cardiac arrest and resuscitation that physiologic quantities of 5% glucose solution administered prior to arrest and resuscitation worsened the neurologic outcome. However, in the clinical context of cardiac arrest and resuscitation, glucose infusion begins during, rather than before, cardiac resuscitation. In another study, Lundy *et al.* demonstrated that the administration of glucose during, and not before, the commencement of ischemia and CPR also resulted in a higher mortality rate and worse neurologic outcome.[106] In addition, more inotrope support was required to maintain blood pressure following resuscitation in animals who received glucose.

The clinical significance of this experimental work is unclear. Nevertheless, its relevance in the setting of human cardiac arrest and resuscitation has been addressed. Longstreth *et al.*,[107] in a retrospective study of neurologic outcome after an out-of-hospital cardiac arrest, demonstrated poorer neurological recovery in patients with a high admission blood glucose. However, in a subsequent study of out-of-hospital CPR patients, these authors suggested that the higher blood glucose levels observed in patients with poorer neurologic outcome might reflect a more prolonged and difficult resuscitation.[108] Since only a minimal amount of glucose, if any, was administered before admission to the hospital, they suggested that the rise in blood glucose levels during CPR was due to the endogenous release of glucose.

In summary, the data in humans is inconclusive regarding the effect of glucose levels on neurological outcome following CPR. Nevertheless, laboratory studies have demonstrated the adverse effects of hyperglycemia in animals suffering cerebral ischemia. Thus, it seems rational to avoid the administration of supplemental glucose during CPR unless hypoglycemia is suggested or is present.

Calcium and Calcium Channel Blockers

The use of calcium during a cardiac arrest has recently come into disrepute, primarily because of the finding that, in the setting of cardiac arrest, calcium may prevent reflow of blood into ischemic areas of the brain and heart, worsening the clinical outcome. In addition, many investigators believe that cytoplasmic calcium accumulation is the final common pathway of cell death.[109,110] Moreover, inhibition of calcium accumulation following an ischemic episode preserves myocardial function,[111] so calcium channel blocking agents may be more effective than calcium itself in preventing or ameliorating damage during or following an ischemic event such as a cardiopulmonary arrest. Calcium channel blockers also have been shown to raise the threshold of the ischemic heart to ventricular fibrillation.[112]

The calcium ion is essential in myocardial excitation-contraction coupling, in increasing contractility, and in enhancing ventricular automaticity during asystole.[113] Because of these physiologic effects, calcium chloride has been recommended in the treatment of electromechanical dissociation and asystole. Evidence for the successful use of calcium in these settings, however, is lacking.[114–116]

At present, the firm indication for the use of calcium during CPR is in treating patients with known hypocalcemia. This condition may be seen in patients with conditions predisposing to a decrease in total body calcium, such as hypoparathyroidism, renal failure, and pancreatitis, or when ionized calcium is decreased following a massive blood transfusion. This is seen most commonly in the operating room in patients undergoing major surgical procedures, after massive trauma, or during orthotopic liver transplantation. Calcium administration in the CPR setting should also be considered for the treatment

of cardiac arrest due to hyperkalemia, hypermagnesemia, and calcium-channel blocker overdose.[116]

In summary, we have attempted to review some of the controversies surrounding the practice of CPR today. There are still many questions regarding the physiologic and pharmacologic principles that affect our clinical practice of CPR. We all anxiously await answers to these questions so that the poor outcome in patients who have been resuscitated from a cardiac arrest can be improved.

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References

1. Kouwenhoven WB, Jude JR, Knickerbocker GG: Closed chest cardiac massage. JAMA 173:1064–1067, 1960
2. Standards for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). JAMA 255:2905–2932, 1986
3. Weale FE, Rothwell-Jackson RL: The efficiency of cardiac massage. Lancet 1:990–992, 1962
4. Rudikoff MT, Maughan WL, Effron M, Freund P, Weisfeldt ML: Mechanisms of blood flow during cardiopulmonary resuscitation. Circulation 61:345–352, 1980
5. Criley JM, Blaufuss AH, Kissel GL: Cough-induced cardiac compression. JAMA 236:1246–1248, 1976
6. Rosborough JP, Hausknecht M, Niemann JT, Criley JM: Cough supported circulation. Crit Care Med 9:371–372, 1981
7. Weisfeldt ML, Chandra N: Physiology of cardiopulmonary resuscitation. Annu Rev Med 32:435–442, 1981
8. Chandra N, Guerci A, Weisfeldt ML, Tsitlik J, LePor N: Contrasts between intrathoracic pressures during chest compression and cardiac massage. Crit Care Med 9:789–792, 1981
9. Niemann JT, Rosborough JP, Hausknecht M, Garner D, Criley JM: Pressure-synchronized cineangiography during experimental cardiopulmonary resuscitation. Circulation 64:985–991, 1981
10. Werner JA, Greene HL, Janko CL, Cobb IA: Visualization of cardiac valve motion in man during external chest compression using two-dimensional echocardiography. Circulation 63:1417–1421, 1981
11. Rich S, Wix HL, Shapiro EP: Clinical assessment of heart chamber size and valve motion during cardiopulmonary resuscitation by two-dimensional echocardiography. Am Heart J 102:368–373, 1981
12. Cohen JM, Chandra N, Alderson PO, Aswegen AV, Tsitlik JE, Weisfeldt ML: Timing of pulmonary and systemic blood flow during intermittent high intrathoracic pressure cardiopulmonary resuscitation in the dog. Am J Cardiol 49:1883–1889, 1981
13. Babbs CF, Tacker WA, Paris RL, Murphy RJ, Davis RW: CPR with simultaneous compression and ventilation at high airway pressure in 4 animal models. Crit Care Med 10:501–504, 1982
14. Weisfeldt ML, Halperin HR: Cardiopulmonary resuscitation: Beyond cardiac massage. Circulation 74:443–448, 1986
15. Maier GW, Tyson GS, Olsen CO, Kernstein KH, Davis JW, Conn EH, Sabiston DC, Rankin JS: The physiology of external cardiac massage: High-impulse cardiopulmonary resuscitation. Circulation 70:86–101, 1984
16. Feneley MP, Maier GW, Gaynor W, Gall SA, Kisslo JA, Davis JW, Rankin JS: Sequence of mitral valve motion and transmitral blood flow during manual cardiopulmonary resuscitation in dogs. Circulation 76:363–375, 1987
17. Kernstine KH, Tyson GS Jr, Maier GW, Olson CO, Davis JW, Rankin JS: Determinants of direct cardiac compression during extended cardiac massage in dogs. Crit Care Med 10:231–234, 1981
18. Deshmukh HG, Weil MH, Rackow EC, Trevino R, Bisera J: Echocardiographic observations during cardiopulmonary resuscitation: A preliminary report. Crit Care Med 13:904–906, 1985
19. Halperin HR, Tsitlik JE, Guerci AD, Mellits ED, Levin HR, Shi AY, Chandra N, Weisfeldt ML: Determinants of blood flow to vital organs during cardiopulmonary resuscitation in dogs. Circulation 73:539–550, 1986
20. Babbs C, Weaver JC, Ralston S, Geddes L: Cardiac, thoracic and abdominal pump mechanisms in cardiopulmonary resuscitation studies in an electrical model of circulation. Am J Emerg Med 2:299–306, 1984
21. Halperin HR, Tsitlik JE, Beyar R, Chandra N, Guerci AD: Intrathoracic pressure fluctuations move blood during CPR: Comparison of hemodynamic data with predictions from a mathematical model. Ann Biomed Eng 15:385–403, 1987
22. Beyar R, Kishon Y, Sideman S, Dinnar V: Computer studies of systemic and regional blood flow mechanisms during cardiopulmonary resuscitation. Med Biol Eng Comput 22:499–506, 1984
23. Fitzgerald KR, Babbs CF, Fressoia HA, Davis RW, Silver DI: Cardiac output during cardiopulmonary resuscitation at various compression rates and durations. Am J Physiol 241:H442–448, 1981
24. Feneley MP, Maier GW, Kern KB, Gaynor JW, Gall SA, Sanders AB, Raessler K, Muhlbaier LH, Rankin JS, Ewy GA: Influence of compression rate on initial success of resuscitation and 24 hour survival after prolonged manual cardiopulmonary resuscitation in dogs. Circulation 77:240–250, 1988
25. Taylor G, Tucker W, Greene H, Rudikoff M, Weisfeldt ML: Importance of prolonged compression during cardiopulmonary resuscitation in man. N Engl J Med 296:1515–1517, 1977
26. Schleien CL, Dean JM, Koehler RC, Michael JR, Chantarojanasiri T, Traystman RJ, Rogers MC: Effect of epinephrine on cerebral and myocardial perfusion in an infant animal preparation of cardiopulmonary resuscitation. Circulation 78:809–817, 1986
27. Sanders AB, Ewy GA, Alferness CA, Taft T, Zimmerman M: Failure of one method of simultaneous chest compression, ventilation, and abdominal binding during CPR. Crit Care Med 10:509–513, 1982
28. Chandra N, Rudikoff M, Weisfeldt ML: Simultaneous chest compression and ventilation at high airway pressure during cardiopulmonary resuscitation. Lancet 1:175–178, 1980
29. Chandra N, Weisfeldt ML, Tsitlik J, Vaghaiwalla F, Snyder LD, Hoffecker M, Rudikoff MT: Augmentation of carotid flow during cardiopulmonary resuscitation by ventilation at high airway pressure simultaneous with chest compression. Am J Cardiol 48:1053–1063, 1981
30. Koehler RC, Chandra N, Guerci AD, Tsitlik J, Traystman RJ, Rogers MC, Weisfeldt ML: Augmentation of cerebral perfusion by simultaneous chest compression and lung inflation with abdominal binding after cardiac arrest in dogs. Circulation 67: 266–275, 1983
31. Luce JM, Ross BK, O'Quin RJ, Culver BH, Sivarojan M, Amory DW, Niskanen RA, Alferness CA, Kirk WL, Pierson LB, Butler

J: Regional blood flow during cardiopulmonary resuscitation in dogs using simultaneous and nonsimultaneous compression and ventilation. Circulation 67:258–264, 1983

32. Berkowitz ID, Chantarojanasiri T, Koehler RC, Schleien CL, Dean JM, Michael JR, Rogers MC, Traystman RJ: Simultaneous compression and ventilation cardiopulmonary resuscitation does not enhance cerebral and myocardial perfusion in an infant model of cardiopulmonary resuscitation. ANESTHESIOLOGY 65: A108, 1986
33. Halperin HR, Guerci AD, Chandra N, Hershkowitz A, Tsitlik JE, Niskanen RA, Wurmb E, Weisfeldt ML: Vest inflation without simultaneous ventilation during cardiac arrest in dogs: Improved survival from prolonged cardiopulmonary resuscitation. Circulation 74:1407–1415, 1986
34. Chandra N, Snyder LD, Weisfeldt ML: Abdominal binding during cardiopulmonary resuscitation in man. JAMA 246:351–353, 1981
35. Niemann JT, Rosborough JP, Ung S, Criley JM: Hemodynamic effects of continuous abdominal binding during cardiac arrest and resuscitation. Am J Cardiol 53:269–274, 1984
36. Sharff JA, Pantley G, Noel E: Effect of time on regional organ perfusion during two methods of cardiopulmonary resuscitation. Ann Emerg Med 13:649–656, 1984
37. Bircher N, Safar P, Stewart R: A comparison of standard "MAST" augmented and open chest CPR in dogs. A preliminary investigation. Crit Care Med 8:147–152, 1980
38. Lee HR, Wilder RJ, Downs P, Massion W, Blank WF: MAST augmentation of external cardiac compression: Role of changing intrapleural pressure. Ann Emerg Med 10:560–565, 1981
39. Lilja GP, Long RS, Ruiz E: Augmentation of systolic blood pressure during external cardiac compression by use of the MAST suit. Ann Emerg Med 10:182–184. 1981
40. Mahoney BD, Mirick MJ: Pneumatic trousers in refractory cardiopulmonary arrest. Ann Emerg Med 13:410–414, 1984
41. Babbs CF, Tacker WA: Cardiopulmonary resuscitation with interposed abdominal compression. Circulation 74 (suppl IV), IV-37–41, 1986
42. Babbs CF: Hemodynamic mechanisms in CPR: A theoretical rationale for resuscitative thoracotomy in non-traumatic cardiac arrest. Resuscitation 15:37–50, 1987
43. Koehler RC, Michael JR: Cardiopulmonary resuscitation, brain blood flow, and neurologic recovery. Crit Care Clinics 1:205–222, 1985
44. Voorhees WD, Babbs CF, Niebauer MJ: Improved oxygen delivery during cardiopulmonary resuscitation with interposed abdominal compressions. Ann Emerg Med 12:128–135, 1983
45. Voorhees WD, Ralston SH, Babbs CF: Regional blood flow during cardiopulmonary resuscitation with abdominal counterpulsation in dogs. Am J Emerg Med 2:123–128, 1983
46. Walker JW, Bruestle JC, White BC, Evans AT, Indreri R, Bialek H: Perfusion of the cerebral cortex by use of abdominal counterpulsation during cardiopulmonary resuscitation. Am J Emerg Med 2:391–393, 1984
47. Berryman CR, Phillips GM: Interposed abdominal compression—CPR in human subjects. Ann Emerg Med 13:226–229, 1984
48. Howard M, Carrubba C, Guinness M, Foss F, Hogan B: Interposed abdominal compression CPR: its effects on coronary perfusion pressure–human subjects. Ann Emerg Med 13:989–992, 1984
49. Kern KB, Carter AB, Showern RL, Voorhees WD, Babbs CF, Tacker WA, Ewy GA: Twenty-four hour survival in a canine model of cardiac arrest comparing three methods of manual cardiopulmonary resuscitation. J Am Coll Cardiol 7:859–867, 1986
50. Mateer JR, Stueven HA, Thompson BM, Aprahamian C, Darin J: Pre-hospital IAC-CPR versus standard CPR: Paramedic resuscitation of cardiac arrests. Am J Med 3:143–146, 1985
51. Weiser FM, Adler LN, Kuhn LA: Hemodynamic effects of closed and open-chest cardiac resuscitation in normal dogs and those with acute myocardial infarction. Am J Cardiol 10:555, 1962
52. Bircher N, Safar P, Stewart R: A comparison of standard, "MAST"-augmented, and open-chest CPR in dogs: A preliminary investigation. Crit Care Med 8:147–152, 1980
53. Sanders AB, Kern KB, Ewy GA, Atlas M, Bailey L: Improved resuscitation from cardiac arrest with open-chest massage. Ann Emerg Med 13:672–675, 1984
54. Sanders AB, Kern KB, Atlas M, Bragg S, Ewy GA: Importance of the duration of inadequate coronary perfusion pressure on resuscitation from cardiac arrest. J Am Coll Cardiol 6:113, 1985
55. Del Guercio LRM, Feins NR, Cohn JD, Coomaraswamy RP, Wollman SB, State D: Comparison of blood flow during external and internal cardiac massage in man. Circ Suppl 31:I171–180, 1965
56. Kern KB, Sanders AB, Ewy GA: Open-chest cardiac massage after closed-chest compression in a canine model: When to intervene. Resuscitation 15:51–57, 1987
57. Thaler MM, Stobie GHC: An improved technique of external cardiac compression in infants and young children. N Engl J Med 269:606–610, 1963
58. Orlowski JP: Optimum position for external cardiac compression in infants and young children. Ann Emerg Med 15:667–673, 1986
59. Phillips GW, Zideman DA: Relation of infant heart to sternum: Its significance in cardiopulmonary resuscitation. Lancet 1: 1024–1025, 1986
60. Babbs CF, Voorhees WD, Fitzgerald KR, Holmes HR, Geddes LA: Relationship of blood pressure and flow during CPR to chest compression amplitude: Evidence for an effective compression threshold. Ann Emerg Med 12:527–532, 1983
61. Dean JM, Koehler RC, Schleien CL, Michael JR, Chantarojanasiri T, Rogers MC, Traystman RJ: Age related changes in chest geometry during cardiopulmonary resuscitation. J Appl Physiol 62:2212–2219, 1987
62. Redding JS, Pearson JW: Evaluation for drugs for cardiac resuscitation. ANESTHESIOLOGY 24:203–207, 1963
63. Pearson JW, Redding JS: Influence of peripheral vascular tone on resuscitation. Anesth Analg 44:746–752, 1965
64. Yakaitis RW, Otto CW, Blitt CD: Relative importance of alpha and beta adrenergic receptors during resuscitation. Crit Care Med 7:293–296, 1979
65. Michael JR, Guerci AD, Koehler RC, Shi AY, Tsitlik J, Chandra N, Niedermeyer E, Rogers MC, Traystman RJ, Weisfeldt ML: Mechanisms by which epinephrine augments cerebral and myocardial perfusion during cardiopulmonary resuscitation in dogs. Circulation 69:822–835, 1984
66. Livesay JJ, Follette DM, Fey KH, Nelson RL, Deland EC, Bernard RJ, Buckberg GD: Optimizing myocardial supply/demand balance with alpha-adrenergic drugs during cardiopulmonary resuscitation. J Thorac Cardiovasc Surg 76:244–251, 1978
67. Schleien CL, Koehler RC, Berkowitz ID, Dean JM, Gervais H, Michael JR, Rogers MC, Traystman RJ: Comparison of phenylephrine and epinephrine on cerebral and myocardial perfusion

and somatosensory evoked potentials during and following cardiopulmonary resuscitation in dogs. Circulation (in press)
68. Holmes HR, Babbs CF, Voorhees WD, Tacker WA, DeGaravilla B: Influence of adrenergic drugs upon vital organ perfusion during CPR. Crit Care Med 8:137–140, 1980
69. Brown CG, Werman HA, Davis EA, Katz S, Hamlin RL: The effect of high-dose phenylephrine versus epinephrine on regional cerebral blood flow during CPR. Ann Emerg Med 16:743–748, 1987
70. Brown CG, Davis EA, Werman RL: Methoxamine versus epinephrine on regional cerebral blood flow during cardiopulmonary resuscitation. Crit Care Med 15:682–686, 1987
71. Ralston SH, Voorhees WD, Babbs CF: Intrapulmonary epinephrine during prolonged cardiopulmonary resuscitation: Improved regional blood flow and resuscitation in dogs. Ann Emerg Med 13:79–86, 1984
72. Schleien CL, Koehler RC, Berkowtiz ID, Dean JM, Michael JR, Rogers MC, Traystman RJ: Effect of phenylephrine on cerebral and myocardial perfusion during cardiopulmonary resuscitation in infant piglets (abstract). ANESTHESIOLOGY 65:A76, 1986
73. Brown CG, Werman HA, Davis EA, Hamlin R, Hobson J, Ashton JA: Comparative effects of graded doses of epinephrine on regional brain blood flow during CPR in a swine model. Ann Emerg Med 15:1138–1144, 1986
74. Brown CG, Birinyi F, Werman HA, Davis EA, Hamlin RL: The comparative effects of epinephrine versus phenylephrine on regional cerebral blood flow during cardiopulmonary resuscitation. Resuscitation 14:171–175, 1986
75. MacKenzie, ET, McCulloch J, O'Keane M, Pickard JD, Harper AM: Cerebral circulation and norepinephrine: Relevance of the blood-brain barrier. Am J Physiol 231:483–486, 1976
76. Carlsson C, Hagerdal M, Kaasik AE, Siesjo BK: A catecholamine-mediated increased in cerebral oxygen uptake during immobilization stress in rats. Brain Res 119:223–231, 1977
77. Edvinsson L, Hardebo JE, MacKenzie ET, Owman C: Effect of endogenous noradrenaline on local cerebral blood flow after osmotic opening of the blood-brain barrier in the rat. J Physiol (Lond) 274:149–156, 1978
78. Lasbennes F, Sercombe R, Seylaz J: Monoamine oxidase activity in brain microvessels determined using natural and artificial substances: Relevance to the blood-brain barrier. J Cereb Blood Flow Metab 3:521–528, 1983
79. Arai T, Watanabe T, Nagaro T, Matsuo S: Blood-brain barrier impairment after cardiac resuscitation. Crit Care Med 9:444–448, 1981
80. Brillman JA, Sanders AB, Otto CW, Fahmy H, Bragg S, Ewy GA: Outcome of resuscitation from fibrillatory arrest using epinephrine and phenylephrine in dogs. Crit Care Med 13:912–913, 1985
81. Winquist RJ, Webb RC, Bohr OF: Relaxation to transmural nerve stimulation and exogenously added norepinephrine in porcine vessels. A study utilizing cerebrovascular intrinsic tone. Circ Res 51:769–776, 1982
82. Berkowitz ID, Koehler RC, Schleien CL, Dean JM, Gervais H, Michael JR, Rogers MC, Traystman RJ: Cerebral and myocardial blood flow response to increasing doses of epinephrine during cardiopulmonary resuscitation in infant swine (abstract). ANESTHESIOLOGY 67:A649, 1987
83. Grundler W, Weil MH, Rackow EC: Arteriovenous carbon dioxide and pH gradients during cardiac arrest. Circulation 74: 1071–1074, 1986
84. Weil MH, Rackow EC, Trevino R, Grundler W, Falk JL, Griffel MI: Differences in acid-base state between venous and arterial blood during cardiopulmonary resuscitation. N Engl J Med 315: 153–156, 1986
85. Cingolani HE, Mattiazi AR, Blesa ES: Contractility in isolated mammalian heart muscle after acid-base changes. Circ Res 26: 269–278, 1970
86. Pannier JL, Leusen I: Contraction characteristics of papillary muscle during changes in acid-base composition of the bathing fluid. Arch Int Physiol Biochim 76:624–634, 1968
87. Poole-Wilson PA, Langer GA: Effect of pH on ionic exchange and function in rat and rabbit myocardium. Am J Physiol 229: 570–581, 1975
88. Berenyi KJ, Wolf M, Killip T: Cerebrospinal fluid acidosis complicating therapy of experimental cardiopulmonary arrest. Circulation 52:319–324, 1975
89. Bygdeman S: Vascular reactivity in cats during induced changes in the acid-base balance of the blood. Acta Physiol Scand 61(suppl 2):1–65, 1963
90. Wood WB, Manley ES Jr, Woodbury RA: The effects of CO_2-induced respiratory acidosis on the depressor and pressor components of the dog's blood pressure response to epinephrine. J Pharmacol Exp Ther 139:238–247, 1963
91. Steinhart CR, Permutt S, Gurtner GH, Traystman RJ: Beta-adrenergic activity and cardiovascular response to severe respiratory acidosis. Am J Physiol 244:H46–54, 1983
92. Stacpoole PW: Lactic acidosis: The case against bicarbonate therapy. Ann Intern Med 105:276–279, 1986
93. Narins RG, Cohen JJ: Bicarbonate therapy for organic acidosis: The case for its continued use. Ann Intern Med 106:615–618, 1987
94. Guerci AD, Chandra N, Johnson E, Rayburn B, Wurmb E, Tsitlik J, Halperin HR, Siu C, Weisfeldt ML: Failure of sodium bicarbonate to improve resuscitation from ventricular fibrillation in dogs. Circulation 74:IV75–79, 1986
95. Graf H, Leach W, Arieff AI: Evidence for a detrimental effect of bicarbonate therapy in hypoxic lactic acidosis. Science 227: 754–756, 1985
96. Misbin RI: Phenformin-associated lactic acidosis: Pathogenesis and treatment. Ann Intern Med 87:591–595, 1977
97. Sessler D, Mills P, Gregory G, Litt L, James T: Effects of bicarbonate on arterial and brain intracellular pH in neonatal rabbits recovering from hypoxic lactic acidosis. J Pediatr 111:817–823, 1987
98. Myers R: Lactic acid accumulation as a cause of brain edema and cerebral necrosis resulting from oxygen deprivation. Advances in Perinatal Neurology. Edited by Korbin R, Guilleminault C. New York, Spectrum, 1979, pp 84–114
99. Ginsberg MD, Welsh FA, Budd WW: Focal cerebral blood flow and glucose utilization. Stroke 1:347–354, 1980
100. Pulsinelli WA, Waldman S, Rawlinson D, Plum F: Moderate hyperglycemia augments ischemic brain damage: A neuropathologic study in the rat. Neurology 32:1239–1246, 1982
101. Lanier WL, Stangland KJ, Scheithauer BW, Milde JH, Michenfelder JD: The effects of dextrose infusion and head position on neurologic outcome after complete cerebral ischemia in primates: Examination of a model. ANESTHESIOLOGY 66:39–48, 1987
102. Combs DJ, Reuland DS, Martin DB, Zelenock GB, D'Alecy LG: Glycolytic inhibition by 2-deoxyglucose reduces hyperglycemic associated mortality and morbidity in the ischemic rat. Stroke 17:990–994, 1986
103. Kraig RP, Petito CK, Plum F, Pulsinelli WA: Hydrogen ions kill

brain at concentrations reached in ischemia. J Cereb Blood Flow Metab 7:379–386, 1987

104. Pulsinelli WA, Levy DE, Sigsbee B, Scherer P, Plum F: Increased damage after ischemic stroke in patients with hyperglycemia with or without established diabetes mellitus. Am J Med 74: 540–544, 1983

105. D'Alecy LG, Lundy EF, Barton KJ, Zelenock GB: Dextrose containing intravenous fluid impairs outcome and increases death after eight minutes of cardiac arrest and resuscitation in dogs. Surgery 100:505–511, 1986

106. Lundy EF, Kuhn JE, Kwon JM, Zelenock GB, D'Alecy: Infusion of five percent dextrose increases mortality and morbidity following six minutes of cardiac arrest in resuscitated dogs. J Crit Care 2:4–14, 1987

107. Longstreth WT, Inui TS: High blood glucose level on hospital admission and poor neurological recovery after cardiac arrest. Ann Neurol 15:59–63, 1984

108. Longstreth WT, Diehr P, Cobb LA, Hanson RW, Blair AD: Neurologic outcome and blood glucose levels during out-of-hospital cardiopulmonary resuscitation. Neurology 36:1186–1191, 1986

109. Katz AM, Reuter M: Cellular calcium and cardiac cell death. Am J Cardiol 44:188–190, 1979

110. White BC, Winegar CD, Wilson RF, Hoehner PJ, Trombley JH: Possible role of calcium blockers in cerebral resuscitation: A review of the literature and synthesis for future studies. Crit Care Med 11:202–207, 1983

111. Clark RE, Kristlieb IY, Henry PD: Nifedipine: A myocardial protective agent. Am J Cardiol 44:825–831, 1979

112. Resnekov L: Calcium antagonist drugs—Myocardial preservation and reduced vulnerability to ventricular fibrillation during CPR. Crit Care Med 9:360–361, 1981

113. Greenblatt DJ, Gross PL, Bolognini V: Pharmacotherapy of cardiopulmonary arrest. Am J Hosp Pharm 33:579–583, 1976

114. Stueven HA, Thompson B, Aprahamian C, Tonsfeldt DJ, Kastenson EH: The effectiveness of calcium chloride in refractory electromechanical dissociation. Ann Emerg Med 14:626–629, 1985

115. Stueven HA, Thompson B, Aprahamian C, Tonsfeldt DJ, Kastenson EH: Lack of effectiveness of calcium chloride in refractory asystole. Ann Emerg Med 14:630–632, 1985

116. Dembo DH: Calcium in advanced life support. Crit Care Med 9:358–359, 1981