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Foreword

Dr. Max Harry Weil is a name that is legendary in critical care medicine. He is one of the founders of modern intensive care. He has led the way in carrying out and pointing out areas of research that produce fruitful results. He is a great teacher in the classroom and lecture hall and by means of journals and textbooks. He continues to be one of our most thoughtful commentators on issues in critical care medicine. With his colleague Dr. Wanchun Tang, Dr. Weil gives us in this issue a truly thought-provoking review of cardiopulmonary resuscitation from its historic beginnings to the present day. Drs. Weil and Tang give us valuable perspective on basic assumptions that underpin our judgment and actions when CPR is required. We learn from Drs. Weil and Tang that an assumption held by many of us regarding CPR—that it is a "settled" matter that requires little or no additional research—is clearly wrong. In light of what they tell us in this issue of *Disease-a-Month*, we can see the many leaps of faith we have made to bridge gaps in our knowledge. The authors are not making a nihilistic attack on CPR. On the contrary, they lead us through the wealth of knowledge manifested in current CPR guidelines and point out areas that need to be strengthened with additional research and put to test in clinical trials when such would be appropriate. The need for more research is reflected in statistics that show little or no improvement in outcome in the 35 years since modern CPR was introduced. We thank Drs. Weil and Tang for this contribution to *Disease-a-Month*.

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Editor-in-Chief
Abstract.—After failure of initial external defibrillation, restoration of spontaneous circulation is largely contingent on rapid and effective reversal of myocardial ischemia by both mechanical and pharmacologic means. Despite the introduction of modern cardiopulmonary resuscitation (CPR) more than 35 years ago, its universal acceptance, and its wide implementation, no improvements in outcome excepting early defibrillation have been documented over these many years. The science of CPR therefore is still in its infancy. It was incorrectly assumed that all that needs to be known is known and that the need for scientific research was therefore not apparent. Accordingly, serious resuscitation research was neither encouraged nor equitably supported. The ABCs of CPR currently provide for the establishment of a patent airway (A) and intermittent positive pressure ventilation, preferably with oxygen-enriched air (B). These are to be immediately followed with precordial compression (C). This ordering of priorities, however, is based on consensus rather than objective outcome measurements. The ABCs recently have been seriously challenged on the basis of results of both experimental and clinical studies.

Conventional external precordial compression restores systemic blood flow. It may be used by both professional and nonprofessional CPR providers, especially bystanders, because of its apparent simplicity and noninvasiveness. However, manual or mechanical external precordial compression typically generates cardiac outputs that represent less than 30% of normal values. Coronary blood flow, which is critical for restoration of spontaneous circulation, is correspondingly reduced. Accordingly, several alternatives to conventional precordial compression have been proposed with the intent of increasing cardiac output and both coronary and cerebral blood flows.

Among the large number of pharmaceutical agents initially recommended for cardiac resuscitation, only agents that produce peripheral vasoconstriction are of proved benefit. Epinephrine has been the preferred vasopressor agent for the management of cardiac arrest for more than 35 years because of its α-adrenergic effects. However, the potentially adverse effects of epinephrine are related to its β-adrener-
gic inotropic actions. The β-adrenergic actions account for disproportionate increases in myocardial oxygen consumption with increased severity of myocardial ischemic injury and provocation of ectopic ventricular tachycardia and ventricular fibrillation. Nevertheless, epinephrine remains the drug of choice, although adrenergic drugs with selective α-adrenergic actions or nonadrenergic vasoconstrictor drugs are likely to emerge as useful alternatives.

Experimental and clinical observations have led to identification of continuous monitoring of both end-tidal carbon dioxide and ventricular fibrillation waveforms as practical noninvasive guides because they are highly correlated with both cardiac output and coronary blood flow. Both end-tidal carbon dioxide and ventricular fibrillation waveforms now serve as predictors of the likelihood of successful resuscitation. These two measurements may now be used to guide interventions and especially to assure optimal precordial compression.

It is well established that sudden death among adults is predominantly due to malignant ventricular arrhythmias and ventricular fibrillation. Early defibrillation serves as an unequivocally effective immediate intervention. Minimally trained first responders and members of the general public are being enfranchised to use automated external defibrillators for very early defibrillation. Use of these devices by bystanders is the most promising new intervention since CPR was first proposed in the early 1960s.

Postresuscitation ventricular dysrhythmias and heart failure are now called postresuscitation myocardial dysfunction. This complication has been recognized as a leading cause of the high postresuscitation mortality rate. More than 80% of victims who undergo successful resuscitation die after admission. Much effort is devoted to the understanding of mechanisms and to defining effective therapeutic options for improving outcomes to reduce the death rate from postresuscitation myocardial dysfunction.
Almost 35 years have elapsed since the combined techniques of mechanical ventilation, external precordial compression, and electrical defibrillation were introduced. These ushered in the modern era of cardiopulmonary resuscitation (CPR). The outcome of CPR intervention after "sudden death" is nevertheless very disappointing. It is estimated that in the United States alone more than 500,000 otherwise functional adults die suddenly each year of cardiac causes predominantly due to acute events caused by coronary artery disease. However, less than 3% of these victims are likely to undergo resuscitation to the extent that they return to an optimal level of functioning.

The current methods of CPR, which followed the landmark publications of the early 1960s by Kouwenhoven and Safar and their associates, provide for clearance of the airway, intermittent positive pressure ventilation, and chest compression as essential interventions. The ABCs of CPR (airway, breathing, and circulation) represent the sequence of interventions currently advised and taught to providers of both basic life support and advanced life support by the American Heart Association. Interventions by which circulation is restored with chest compression (or alternative mechanical means) remain the lowest priority. This ordering of priorities, however, is based on consensus rather than objective experimental or clinical evidence of improved outcome. During the last 5 years, both experimental and clinical studies demonstrated that the A and B of the ABCs, specifically positive-pressure ventilation, may not be essential during the initial 6 to 12 minutes of CPR under conditions of sudden dysrhythmic cardiac arrest in the absence of asphyxia. More recent studies provide additional evidence that either precordial compression or spontaneous gasping may generate sufficient alveolar ventilation such that adequate alveolar gas exchange is maintained without positive-pressure ventilation.

The current conventional techniques of external precordial compression generate a cardiac output that is typically less than 25% of normal. Accordingly, research focuses on options by which the hemodynamic efficacy of CPR may be increased. Promising new methods have emerged. These include interposed abdominal compression, active compression-decompression, circumferential chest compression, intermittent ascending aortic balloon occlusion, extracorporeal circulation, and most recently, phased chest and abdominal compression-decompression. Although there is as yet no persuasive evidence that any of these new methods has improved the long-term outcome of cardiac arrest for human victims, there is promise of hemodynamically more effective closed-chest interventions by which the severity of global myocardial ischemia during CPR is lessened and outcomes are improved.
Pharmacologic interventions, especially with adrenergic agents, increase arterial resistance and thereby redirect systemic blood flow predominantly to the coronary and cerebral arteries. They improve coronary perfusion and cerebral perfusion. A threshold level of coronary perfusion pressure is estimated to be 15 mm Hg, the prerequisite for restoration of spontaneous circulation. Both adrenergic and nonadrenergic vasopressor drugs are of potential value. The intent is to produce systemic vasoconstriction, increasing aortic diastolic aortic pressure and thereby coronary perfusion pressure. These vasopressor agents provide preferential blood flow to the heart and brain. Yet persistent vasoconstrictor effect after restoration of spontaneous circulation adversely affects ventricular function by increasing afterload.

The β effect of epinephrine accounts for increases in atrial and ventricular automaticity, decreases in the effective refractory period of the ventricles, and increases in myocardial oxygen consumption. These increase the incidence of postresuscitation ventricular arrhythmias and myocardial ischemic injury. The relatively selective α₁-adrenergic agents prolong the effective refractory period of the ventricular myocardium and thereby minimize postresuscitation ventricular dysrhythmias. However, down regulation of α₁-adrenergic receptors during CPR may explain the lesser effectiveness of selective α₁-adrenergic agents as vasopressor agents over time. Epinephrine, which stimulates both α₁- and α₂-adrenergic receptors, remains the drug of choice despite its potentially detrimental β-adrenergic effects.

Ventricular fibrillation has been the predominant cause of death among adults. Electrical defibrillation is therefore the most important initial intervention for improving survival. However, defibrillation must be accomplished within the first minute or two after collapse. Automated external defibrillators, which were first introduced some 15 years ago, are now perceived as an important breakthrough. These automated devices allow nonmedical first responders or members of the general public to undertake early defibrillation. This has created the promise of greater survival rates. Postresuscitation myocardial dysfunction and its fatal progression may be related, in part, to injury produced by the high power of the delivered electric shock. Biphasic waveform defibrillation has the dual advantage of lesser delivered energy for successful defibrillation and greater portability of the device itself.

Although regional postischemic myocardial dysfunction associated with coronary artery occlusion has been extensively investigated, little is known regarding the changes in myocardial function that follow reversal of global myocardial ischemia after successful resuscitation from cardiac arrest.
Observations on experimental animals and anecdotal reports of human victims of cardiac arrest support the concept that reversible systolic and diastolic dysfunction evolves early after resuscitation from cardiac arrest. Reversible postresuscitation myocardial dysfunction representing both myocardial contractile failure and life-threatening ventricular ectopic dysrhythmias account for the high fatality rate in the early hours and days after successful resuscitation. Nevertheless, the pathophysiologic and clinical courses of postresuscitation myocardial dysfunction are not as yet fully understood.
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Dr. Weil began a distinguished career at southern California institutions as chief of cardiology, City of Hope Medical Center, Duarte. From 1957 to the present he has held clinical and academic positions at the University of Southern California School of Medicine, including director of the shock research unit; director of the Center for the Critically Ill; professor of biomedical engineering; and chairman of the division of critical care medicine. Dr. Weil also has served as chairman, Los Angeles County Commission on Emergency Medical Services. From 1981 to 1991 he was professor and chairman of medicine, professor of physiology and biophysics, and chief, divisions of cardiology and critical care medicine, University of Health Sciences, The Chicago Medical School.

Dr. Weil has been president of the Institute of Critical Care Medicine since 1974. He holds memberships in numerous national and international medical and scientific organizations. As a reflection of his expertise and interest in cardiology, critical care medicine, and physiology, Dr. Weil has headed many councils and committees directed at topics in those areas, including the American Heart Association and the American College of Cardiology. Dr. Weil has been awarded a number of patents for devices used in critical care medicine. A much sought-after teacher and lecturer, he has been invited lecturer or faculty at many institutions all over the world. Dr. Weil's prolific research also is reflected in his more than 950 publications and nine patents on critical care-related instrumentation.
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History of Cardiopulmonary Resuscitation

The history of cardiopulmonary resuscitation (CPR), which began in ancient times, is remarkably illuminating. The history has been recited in some detail by members of our group. Cardiopulmonary resuscitation is described in the Old Testament. To quote I Kings 17,

And it came to pass that the son of the woman fell sick and his sickness was so sore that there was no breath left in him.... He stretched himself upon the child three times and cried unto the Lord and the Lord heard the voice of Elijah. And the soul of the child came into him again and he revived.

The following is from II Kings 4,

When Elisha was come into the house, he saw the child lying dead upon his bed. So he went in and shut the door upon the two of them and prayed to the Lord. Then he went up and lay upon the child and put his mouth upon his mouth and his eyes and his hands upon his hands and he stretched himself upon the child and the flesh of the child waxed warm.

These descriptions quite vividly relate the use of both chest compression and mouth-to-mouth ventilation with successful restoration of life. We now review salient history with reference to current priorities established by the American Heart Association and especially the ABCs of CPR.

Airway: A

The earliest description of methods by which the airway was secured was recorded in the Babylonian Talmud between 200 B.C. and A.D. 400. The Talmud describes a lamb that sustained an injury to the neck such that a large hole was made in the trachea. A tubular, hollow reed was inserted into the trachea to sustain the animal's breathing, and the lamb survived.

Andreas Vesalius of Belgium (1514–1564) gained fame as an anatomist during the Renaissance, which coincided with the dawn of modern medical science. Vesalius systematically dissected human bodies, and from his
surprisingly precise investigations, in 1543 he published the first comprehensive textbook of human anatomy. Vesalius documented that tracheostomy, insertion of a tubular reed into the tracheal ostium of live dogs and pigs not unlike the Talmudic description allowed adequate air exchange. When the tubular reed was connected to a bellows, the lungs were mechanically distended with air during inflation. It is apparent that this very early scientist had already made a transition from anatomy to physiology with appreciation of the functions of the airway and ventilation.

Establishment of an airway has continued to be regarded as the priority during resuscitation. Endotracheal intubation is therefore widely recognized as the appropriate intervention for securing the airway during advanced life support. The first person on record as demonstrating endotracheal intubation as a method of resuscitation was Benjamin Pugh, a surgeon. He made an early version of an endotracheal tube, called an air pipe, from a coiled wire covered with soft leather. Pugh inserted the endotracheal tube through the mouth of neonates for resuscitation when asphyxiation was suspected. In 1754, the method was regarded as effective for ventilation. Blind oral intubation with this air pipe, however, proved both technically difficult and traumatic to the larynx because the vocal chords were not visualized.

During the 18th century, voluntary societies were established in large European cities and later in New York and Boston that sought to improve methods of resuscitating drowning victims. The Society for Recovery of Drowned Persons established in Amsterdam, for instance, developed a protocol for resuscitation. The protocol directed that the victim’s head be positioned lower than the legs to allow swallowed water to drain and, at the same time, reduce risk for aspiration. This ushered in modern efforts to protect the airway during CPR.

During the latter part of the 18th century, after it was recognized that most drowning victims aspirate little water, emphasis on the head-down position was abandoned. Laryngospasm subsequently was implicated as the more probable cause of fatal respiratory failure. The Humane Society of the State of New York therefore focused on ventilation. Mouth-to-mouth or mouth-to-nose ventilation was rediscovered and recommended. The rediscovered practice of inserting a tube into the trachea to allow a bellows to be used for artificial ventilation ushered in modern methods of endotracheal intubation and positive-pressure ventilation.

The problem of upper airway obstruction was addressed by Goodwyn in 1783. He described obstruction of the upper airway in a comatose patient and concluded that the obstruction was caused by a flaccid tongue. In 1869, Benjamin Howard emphasized the importance of securing the airway. He advocated that the tongue of a drowning victim be extended manually to
prevent obstruction of the airway during ventilation. During the same year, Joseph Clover, an early anesthetist, also identified upper airway obstruction. He recommended Henry R. Silvester’s manual ventilation method, which was intended to prevent upper airway obstruction. In 1875 Esmarch and Heiberg recommended that the mandible be moved forward by the resuer to open the air passage. These innovations allowed improved outcomes during resuscitation efforts on drowning victims. When a patent airway was secured and artificial ventilation initiated, effective gas exchange was maintained.

After introduction of Pugh’s tube, several metal tubes were introduced during the 18th century, but none overcame the difficulty of blind insertion of stiff tubes and resulting injuries to the airway. It was not until the 19th century, after the introduction and widespread application of gaseous anesthesia for surgical operations, that aspiration pneumonia became a serious problem. This prompted a more serious effort to secure the airway. Friedrich Trendelenburg, a German surgeon, in 1885 invented a tracheotomy tube with an inflated cuff for this purpose. An endotracheal tube was designed by Eisenmenger in 1893 to include an inflatable cuff. However, the difficulty of manual intubation was resolved only after Chevalier Jackson introduced the laryngoscope in 1920, on the basis of an earlier invention by Kirstein in 1910. Oral intubation was perfected in such a way that it became relatively facile and nontraumatic. This accounted for wide acceptance of oral intubation for securing the airway in a diversity of settings, including general anesthesia and resuscitation.

Safar et al. in 1959 recognized the advantages of endotracheal intubation for routine positive-pressure ventilation in settings of cardiopulmonary resuscitation. After endotracheal intubation, tidal volume generated by positive-pressure ventilation was markedly increased over that produced with mask ventilation. Endotracheal intubation subsequently became routine in anesthesia settings and a high priority for CPR. Safar et al. reintroduced methods for minimizing airway obstruction during CPR. They emphasized the head tilt for extending the atlantooccipital joint together with forward displacement of the mandible to open the airway.

Breathing: B

One of the earliest descriptions of artificial ventilation was from Egyptian mythology. According to Jayne, Isis resuscitated her dead husband Osiris by breathing into his mouth. The other early description of artificial ventilation by the prophet Elisha, who was the disciple of Elijah, in 800 B.C. is cited earlier. For practical purposes, Elisha’s method of resuscitation was mouth-to-mouth ventilation.
Bellows were used in ancient times for sustaining fires for heating or cooking. According to Thangham et al.,
mechanical ventilation of the lungs with bellows was practiced as early as A.D. 175 by Galen of Greece. In his experiments Galen used bellows to inflate the lungs of a dead animal. Studies on pigs and monkeys by this early scientist and philosopher established both anatomic and physiologic concepts of lung function. Although he wrote more than 20 volumes that greatly influenced the practice of medicine for the next 1300 years, Galen’s science was intermingled with both philosophy and religion.

In the 16th century, Paracelsus used bellows to blow air directly into one nostril of a dying patient. An assistant blocked air escape from the other nostril and from the mouth, thereby generating high airway pressures. This method injured the lungs because of barotrauma generated by high airway pressures. In more scientific studies of the anatomy and physiology of the respiratory system, Hooke maintained the heartbeat of a dog whose chest was open for hours when the bellows were used more optimally to sustain ventilation. Hooke incidentally proved that movement of the heart and inflation of the lungs were independent of each other.

Advances in artificial ventilation during the 18th century were prompted by the need for lifesaving interventions after drowning or smoke inhalation, which were leading causes of sudden death at the time. In 1744, William Tossach reported on a case of smoke inhalation that induced cardiac arrest. The victim underwent successful resuscitation by means of mouth-to-mouth ventilation, as follows:

I applied my mouth close to his and blew my breath as strong as I could, but having neglected to stop up both his nostrils, all the air came out of them. I took hold of them with one hand, and I again blew my breath as strong as I could raising his chest fully. Immediately I felt six or seven beats of the heart.

The victim regained consciousness and recovered.

Mouth-to-mouth resuscitation has continued to serve as an important option for artificial ventilation during CPR. The mouth-to-mouth method can be performed without ancillary equipment, with minimal training, and with apparent benefit. During the latter half of 18th century, the importance of artificial ventilation for resuscitation was well recognized. Both the Dutch Humane Society and the Royal Humane Society of England recommended that either bellows or mouth-to-mouth methods of artificial ventilation be used for resuscitation of breathless (and pulseless) patients. A high incidence of complications caused by bellows, especially pneumothorax, made the bellows method increasingly unpopular.

During the latter 19th century and early 20th century, several methods of ventilation by means of external methods were introduced. In 1858, Henry
Silvester placed the victim in a supine posture with arms extended above the head to increase the capacity of the thorax and allow for greater inspired gas volumes. The arms were then rotated and placed on the chest, compressing the chest to facilitate expiration. In 1869, Benjamin Howard, a New York surgeon, introduced a so-called direct method. The method involved placing the victim on his or her back while a rescuer extended the tip of the tongue out of the mouth. A second rescuer knelt astride the victim's hips and compressed the upper abdomen and ribs at a frequency of 15 compressions per minute.

In 1890, Edward Schafer in England demonstrated that inadequate tidal volumes were generated with the Silvester and Howard methods. Schafer performed studies on animal models (dogs), human cadavers, and healthy human subjects. As an alternative Schafer proposed the prone-pressure technique in which the lower ribs of the prone victim were intermittently compressed. He reported that tidal volumes of approximately 500 ml were generated with this method. The Schafer method became the standard of practice in the United States and Europe during the beginning of the 20th century. The next development was the Holger Nielsen method of artificial ventilation in 1932. One rescuer was positioned at the head of the victim. This rescuer lifted the arms of victim for inspiration and compressed the upper back for expiration. The tidal volume generated with this method ranged from 400 to 1700 ml. This method was adopted as a standard of first aid in both the United States and Europe.

During the 1950s, the popularization of mouth-to-nose and mouth-to-mouth ventilation by James Elam and Peter Safar ushered in the modern era of artificial ventilation. Elam documented normal arterial blood oxygen and carbon dioxide tension when patients under anesthesia, and after neuromuscular blockade with curare, were administered mouth-to-mask or mouth-to-endotracheal tube ventilation. Safar et al. demonstrated the applicability of the mouth-to-mouth method with measurements from unconscious human subjects given curare in the absence of endotracheal intubation. The mouth-to-mouth method proved much more effective than the arm lift and chest pressure methods.

**Artificial Circulation: C**

The earliest report of successful resuscitation by closed chest compression was by John Balassa, a surgeon in Hungary in 1858. During the examination of an 18-year-old woman with asphyxia caused by tubercular laryngeal edema, the patient's respiration and pulse abruptly stopped. Balassa immediately performed laryngotomy and compressed the chest wall with one hand. After approximately 6 minutes of intermittent compression, the pulse and consciousness were restored.
In 1892, Friedrich Maass reported on two successful resuscitations with external chest compression. The first case was that of a 9-year-old boy who was to undergo repair of a cleft palate. During anesthesia with chloroform, the patient became cyanotic, the pupils became widely dilated, and the pulse became impalpable. Maass initiated precordial compression at a rate of 30 to 40 compressions per minute but without apparent benefit. He then compressed the chest “very fast and vigorously....The pupils became constricted, smaller and slow, gasping respiration started up again.” The second case was that of an 18-year-old man with tubercular disease of the right hip joint. An operation on the hip joint was complicated by cardiac arrest. Maass started chest compressions at 120 or more compressions per minute. The carotid artery pulse became palpable within 30 minutes.

In 1904, the renowned surgeon and physiologist George Crile in Cleveland, Ohio, reported another case of successful resuscitation by means of precordial compression. A 28-year-old woman had cardiac arrest during surgical removal of a large goiter. Crile immediately started chest compression. “After an interval of between five or six minutes the heart slowly began to recover its beat and circulation was re-established.” These successful resuscitations led to more serious interest in chest compression for restoring spontaneous circulation. Nevertheless, the potential value of advanced life support was largely ignored by the medical societies until it was rediscovered in the 1960s.

Objective proof that artificial circulation could be produced by means of external chest compression during cardiac arrest came from the surgical laboratories of Johns Hopkins University in 1960. Serendipity provided the observation of its effectiveness. Professor William Kouwenhoven, the retired dean of engineering, and engineer Guy Knickerbocker, Kouwenhoven’s research fellow, sought to examine how long a dog’s heart could remain in ventricular fibrillation and still convert to a regular rhythm after delivery of an electric shock. When Knickerbocker applied the paddles of the defibrillator firmly on the chest of an anesthetized dog after onset of ventricular fibrillation, these well-trained observers observed a transient increase in the directly recorded arterial pressure. They immediately recognized that a force applied to the chest produced movement of blood to the extent that an arterial pressure pulse was generated during ventricular fibrillation. They further demonstrated that by repeatedly applying such a force to the chest, the time frame for successful defibrillation was extended from 1 minute to several minutes. Joined by Dr. James Jude, a surgical resident at the time, the investigators applied this technique to 20 patients who sustained cardiac arrest at the Johns Hopkins Hospital. Four-
teen of these 20 patients underwent successful resuscitation by means of chest compression, and these patients were discharged alive from the hospital. These rediscoveries of defibrillation and chest compression were combined with airway and breathing as part of CPR. This led to the American Heart Association's consensus on the ABCs of cardiac resuscitation. Airway protection, mouth-to-mouth ventilation, and precordial compression were the elements that initiated the modern era of CPR.

**Electrical Defibrillation:**

For centuries, no ready explanation was forthcoming for the sudden collapse and instantaneous death of victims of "sudden death." During the early 19th century, it was assumed that sudden death or "cardiac failure" as it was then commonly called was caused by sudden stoppage of a heart in diastole. Though ventricular fibrillation of a dog heart was first described in 1850 by the Germany physiologist Carl Ludwig, it was considered only a laboratory phenomenon and not viewed as relevant to clinical medicine.

In 1889, John MacWilliam in Aberdeen, Scotland, proposed a then startling hypothesis, namely that the cause of sudden death was ventricular fibrillation. This greatly influenced cardiac resuscitation research and clinical application for the next 100 years. To quote this remarkable physician, "Sudden cardiac failure does not usually take the form of a simple ventricular standstill in diastole.... It assumes, on the contrary, the form of violent, though irregular and uncoordinated, manifestation of ventricular energy. Instead of quiescence, there is a tumultuous activity, irregular in its character and wholly ineffective." This hypothesis was based on experiments on animals but theoretic with respect to patients. It must be remembered that the clinical electrocardiogram (ECG) had not yet been introduced. Sir Thomas Lewis, the leading British physiologist-cardiologist of the early part of the 20th century, regarded MacWilliam's hypothesis as nothing less than "brilliant for his time."

In 1899, the French physiologists Jean Louis Prevost and Frederic Battelli demonstrated that ventricular fibrillation could be terminated with a high-voltage current. Voltage ranged from 240 to 4800 volts, and the current was applied between an electrode placed on the head and a second electrode inserted into the rectum of dogs. In 1930, Hooker et al. demonstrated that ventricular fibrillation could be reversed by means of closed-chest defibrillation of dogs. Carl Wiggers at Western Reserve University, Cleveland, Ohio, resuscitated dogs from ventricular fibrillation in the experimental laboratory in 1940 by means of a combination of open chest cardiac massage and electrical defibrillation. However, he feared that danger
of electrocution for patient or operator with such high-current defibrillation precluded its application on patients. Wiggers concluded that though such an achievement was not impossible, he anticipated no early breakthroughs.\textsuperscript{13}

Seven years later, Claude Beck, a pioneer cardiothoracic surgeon also at Western Reserve University, first spoke of "hearts too good to die." Beck quite promptly demonstrated the clinical application of Wiggers's work. He successfully resuscitated a patient by means of internal cardiac massage and electrical defibrillation. The patient was a 14-year-old boy. During thoracoplasty for repair of a congenital deformity of the chest, the youngster sustained cardiac arrest. An ECG confirmed ventricular fibrillation. Beck began internal cardiac massage. The defibrillator arrived in the operating room only 45 minutes later! The initial shock was unsuccessful, but the second electric shock converted ventricular fibrillation into a supraventricular rhythm and restored spontaneous circulation. The youth recovered uneventfully and without neurologic damage.\textsuperscript{14}

Early clinical defibrillators used an alternating current. The defibrillator unit was physically large and heavy, making it cumbersome and unsuitable for rapid transport. In 1962, Bernard Lown of Boston's Peter Bent Brigham Hospital reported on the advantage of direct-current defibrillation and the use of a direct-current defibrillator. The direct-current defibrillator decreased the need for a large-capacity transformer and therefore allowed manufacture of substantially lighter and smaller defibrillators. The mobile direct-current defibrillator then emerged as the standard for defibrillation of victims of cardiac arrest. The greatest initial impact was for use on patients with acute myocardial infarction. This prompted Pantridge and Geddes in Dublin, Ireland,\textsuperscript{15} to initiate mobile coronary care. Defibrillation allowed an impressive decrease in 48-hour mortality among patients with ischemic heart disease; witnessed cardiac arrest due to ventricular fibrillation was almost immediately reversed with prompt defibrillation.

**Reordering the ABCs of CPR**

More than 500,000 Americans die each year after unexpected, out-of-hospital cardiac arrest. Approximately 85\% of these instances of cardiac arrest occur without warning among patients older than 35 years. These represent instances of sudden death due to dysrhythmic causes, predominantly ventricular fibrillation.\textsuperscript{16} The remarkable advances in defibrillation notwithstanding, the overall survival rates after out-of-hospital cardiac arrest are still disappointing. In Chicago, only 114 of 6541 cardiac arrest victims (1.7\%) survived.\textsuperscript{17} Outcomes were equally dismal in New York, Los Angeles, Detroit, San Francisco, and Paris, France. These poor outcomes re-
flect the small time frame within which CPR is effective. The likelihood of survival is estimated to decrease between 5% and 10% per minute after the onset of cardiac arrest, although there is evidence that this is not a linear function. Rapid implementation of CPR therefore emerges as the highest priority. This was the incentive for Eisenberg et al. to initiate a program of bystander-initiated CPR in which there was emphasis on training of the general public. These priorities also prompted the provision for training and equipment that allowed first-response fire department personnel to perform defibrillation in the field. Responsibility was expanded to the general public and ultimately to paramedics. Early response by a well-organized emergency medical system was secured. The overall survival rate after cardiac arrest in Seattle increased impressively to 18.3%.

The current ABCs of CPR followed the landmark publications in the early 1960s by Kouwenhoven et al. and management of the airway by Safar et al. as described earlier. These methods of securing the airway and starting positive-pressure ventilation were viewed as essential components of CPR by its pioneers. These priorities were translated in a series of consensus statements by the American Heart Association that appeared as Standards and more recently as Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiac Care in 1974, 1980, 1986, and most recently in 1992. The ABCs of CPR—airway, breathing, and circulation (compression)—are now firmly established as the primary sequence of initial interventions for providers of both basic life support (BLS) and advanced cardiac life support (ACLS). Recent versions of the Guidelines provide for a compromise. In settings of suspected or confirmed ventricular fibrillation, external electrical countershock may take precedence over the conventional ABCs. Chest compression (or alternative mechanical means) for restoring circulation still has a lower priority for both BLS and ACLS providers as currently recommended by the American Heart Association and the American Red Cross. This ordering of priorities admittedly is based on a consensus of experts and makes no claim of being based on objective experimental or clinical data that would confirm better outcomes.

Recent data mostly from experimental studies persuade us that precordial compression would now best be regarded as the second priority, immediately after attempts at electrical defibrillation have failed in settings of sudden death. We exclude asphyxia, which typically is promptly identified among victims of witnessed cardiac arrest, because patients experience progressive respiratory distress over minutes and do not have sudden loss of circulation. Both experimental and clinical studies have demonstrated that if ventricular fibrillation is not reversed with an electrical coun-
tershock, critical levels of cardiac output and therefore pulmonary and coronary blood flow must first be restored. When coronary perfusion and myocardial blood flow are increased by means of external chest compression, the success of direct-current defibrillation is correspondingly increased.24-26

The ABC ordering of priorities was first challenged during the latter part of the 1980s because of the following series of three observations. First, during CPR, conventional precordial compression generates a cardiac output that approximates only 25% of physiologic resting values. Accordingly, there is a remarkably small requirement for ventilation to maintain optimal ventilation-perfusion relations. Arterial carbon dioxide tensions are typically reduced to surprisingly low levels of less than 20 mm Hg during CPR because ventilation exceeds the minute volumes required for normal gas exchange in settings of low pulmonary blood flow.27 Second, there is substantial reluctance on the part of rescuers to perform mouth-to-mouth ventilation on persons with cardiac arrest because of the fear of human immunodeficiency virus (HIV) and other transmittable infections.28-30 Third, the current ABCs of CPR represent relatively complex psychomotor tasks for the general public, and it is therefore difficult for providers to learn, perform, and retain competence in performance of the procedures without prompting.31

Our group first demonstrated on a porcine model that there is a remarkable paradox of blood gases between blood sampled from the central venous site and blood from the arterial site during cardiac arrest and CPR.32 Hypercarbic acidosis in mixed venous blood to levels exceeding 60 mm Hg contrasted to hypocarbic alkalosis in arterial blood to levels of 15 mm Hg. Arterial PCO₂ rapidly decreased from a baseline of 40 mm Hg to 20 mm Hg after cardiac arrest and 2 minutes after initiation of CPR (Fig. 1). It was maintained at this level for the ensuing 16 minutes of CPR. Sanders et al.,33 with a canine model of cardiac arrest and resuscitation, confirmed that there were marked decreases in arterial PCO₂ during CPR. Venous hypercarbia and arterial hypocarbia were immediately reversed after restoration of spontaneous circulation. Essentially the same changes in blood gases were demonstrated among patients.27 These studies demonstrated that arterial respiratory alkalosis maintained near-normal pH even though metabolic acidosis appeared during CPR. High ventilation-perfusion ratios accounted for respiratory alkalosis and perfusion failure with lactic acidosis accounted for metabolic acidosis.

The willingness of rescuers to perform mouth-to-mouth ventilation on victims of cardiac arrest has been investigated by several groups. Ornato et al.28 surveyed nearly 1800 BLS instructors in Virginia. These investiga-
FIG. 1. Aortic (AO), pulmonary arterial (PA), right atrial (RA), and great cardiac vein (GCV) blood Pco₂ (mm Hg) after 4 minutes of cardiac arrest and 8 minutes of cardiopulmonary resuscitation.

Tors sought to assess the impact of the acquired immunodeficiency syndrome (AIDS) epidemic and fear of hepatitis virus infection on the willingness of these rescuers to perform mouth-to-mouth ventilation. Only 49% had personally performed CPR during the immediately preceding 3 years, and 40% of that subgroup on at least one occasion had hesitated performing mouth-to-mouth ventilation. Because of fear of transmissible diseases, most respondents would hesitate or would decline performing mouth-to-mouth ventilation on strangers. Even more striking were the results of a study reported by Brenner and Kauffman. The authors surveyed both internists and nurses regarding their willingness to perform mouth-to-mouth ventilation. Only 45% of physicians declined performing mouth-to-mouth breathing, but 80% of nurses declined, again because of the fear of acquiring an infectious disease, especially HIV. A study by Locke et al. revealed that only 15% of respondents would unhesitatingly provide mouth-to-mouth ventilation to strangers, although 68% would not hesitate to perform chest compression. The reality is that rescuers hesitate or decline to perform mouth-to-mouth ventilation because of concern about transmission of disease to the rescuer.

The ABCs of CPR are of themselves challenging to the extent that they involve relatively complex psychomotor tasks, especially one-rescuer CPR.
Weaver et al.\textsuperscript{34} found disappointing decrements in retention of CPR interventions and skills by members of the general public who were trained with a 4-hour course of BLS only 6 months earlier. Another study of skills included medical residents, registered nurses, and members of the general public who were trained 4 to 12 months earlier. Measurements were made on recording mannequins. These demonstrated a decline in overall performance of physicians and nurses to a level comparable with that of the general public. No physicians or nurses and only one person who was not a medical professional performed each step of the ABCs of CPR both in the prescribed sequence and correctly. No intergroup differences in capability to perform mouth-to-mouth ventilation were demonstrated. All performed poorly.\textsuperscript{31}

The foregoing realities prompted reexamination of the priorities of CPR. First addressed was ventilation. Three independent groups of experimental investigators confirmed that positive-pressure ventilation was not essential during the initial 6 to 12 minutes of CPR.\textsuperscript{35-39} Precordial compression without mechanical ventilation for 8 minutes was accompanied by increases in arterial P\textsubscript{CO\textsubscript{2}} from an average of 32 mm Hg to 68 mm Hg. However, hypercapnia of this magnitude did not compromise the success of defibrillation, postresuscitation myocardial function, 24-hour survival, or neurologic outcome.\textsuperscript{35,36}

A coincidental but potentially important discovery was the effect of what has been named agonal gasping. This phenomenon is discussed in greater detail later. However, gasping of itself maintained a minute volume of 3.9 L, approximately 60\% of the prearrest levels of anesthetized, spontaneously breathing animals. Because cardiac output is only 25\% of control values during CPR, these minute volumes maintained adequate ventilation-perfusion relations and sufficient alveolar ventilation. When oxygen was delivered to the airway with an open system, arterial P\textsubscript{O\textsubscript{2}} was maintained at approximately 140 mm Hg, and P\textsubscript{aCO\textsubscript{2}} increased from baseline levels of 39 to only 48 mm Hg by the eighth minute of CPR in studies on swine (Table 1). The success of the resuscitation effort itself, 24- and 48-hour survival rates, and neurologic recovery were the same for both ventilated and nonventilated animals. This finding contrasted to that for animals that breathed only room air during CPR. Increases in the concentration of inspired oxygen improved resuscitation considerably. However, there was no demonstrable improvement in outcomes with positive-pressure ventilation.\textsuperscript{37}

An equally important study on dogs was reported by Chandra et al.\textsuperscript{38} Precordial compression without additional ventilation decreased rather than increased arterial P\textsubscript{CO\textsubscript{2}} during the initial 10 minutes of CPR. Neither arte-
TABLE 1. Blood gases during cardiopulmonary resuscitation without mechanical ventilation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>PC2</th>
<th>PC8</th>
</tr>
</thead>
<tbody>
<tr>
<td>PacO₂ (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>38 ± 3</td>
<td>33 ± 3</td>
<td>28 ± 3*</td>
</tr>
<tr>
<td>B</td>
<td>39 ± 5</td>
<td>37 ± 9</td>
<td>48 ± 19</td>
</tr>
<tr>
<td>PacO₂ (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>87 ± 8</td>
<td>165 ± 82</td>
<td>200 ± 106</td>
</tr>
<tr>
<td>B</td>
<td>90 ± 8</td>
<td>215 ± 144</td>
<td>141 ± 81</td>
</tr>
<tr>
<td>PvcO₂ (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>46 ± 2</td>
<td>57 ± 6</td>
<td>56 ± 9*</td>
</tr>
<tr>
<td>B</td>
<td>49 ± 2</td>
<td>62 ± 8</td>
<td>71 ± 11</td>
</tr>
<tr>
<td>Pvo₂ (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>56 ± 3</td>
<td>34 ± 4</td>
<td>32 ± 5</td>
</tr>
<tr>
<td>B</td>
<td>59 ± 7</td>
<td>36 ± 3</td>
<td>41 ± 9</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

*p < 0.05 versus B.

PC2 and PC8, second and eighth minutes of precordial compression.

A, positive pressure ventilation with oxygen; B, spontaneous breathing with oxygen.

rrial hypercarbia nor hypoxemia was observed when effective precordial compression was maintained over that time period. Finally, a study on pigs by Berg et al.39 further supported the conclusion that mechanical ventilation during cardiac arrest does not improve resuscitation, 24-hour survival rate, or neurologic outcome after 12 minutes of CPR (Table 2).

The applicability of these data to care of patients was supported by Cohen et al.,40 who observed minute volumes of 6 L/min when a combination of precordial compression and decompression was used in the absence of positive-pressure ventilation. The Cerebral Resuscitation Group of Belgium found no statistically significant differences in outcomes among patients revived by bystanders, whether or not mouth-to-mouth ventilation was performed in addition to chest compression.41 As yet, no controlled studies with human subjects have been completed that confirm (or refute) that positive-pressure ventilation improves outcome when it is used during the initial 10 minutes of CPR.

Observations by our group during studies on agonal gasping during CPR provided additional insights.42 We observed that so-called agonal gasps substantially augment pulmonary gas exchange in both rat and pig models of cardiac resuscitation. During spontaneous gasping, the neck, jaw, and tongue are repositioned to maintain unobstructed flow of gas in the airway. Both gasp volumes and simultaneous measurements of intrathoracic pressure indicate that this free passage of gas through the airway during typical gasping also produces forward blood flow, most likely the effects of increases in intratho-
TABLE 2. Outcomes of cardiopulmonary resuscitation without mechanical ventilation

<table>
<thead>
<tr>
<th>Intervention</th>
<th>No. resuscitated</th>
<th>No. with 24-hr survival</th>
<th>Neurologic deficit *</th>
<th>Energy (joules)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E, V, C</td>
<td>16/16</td>
<td>16/16</td>
<td>0</td>
<td>103 ± 136</td>
</tr>
<tr>
<td>C</td>
<td>16/16</td>
<td>16/16</td>
<td>2 ± 8</td>
<td>116 ± 135</td>
</tr>
<tr>
<td>None</td>
<td>8/8</td>
<td>2/8*</td>
<td>123 ± 173†</td>
<td>713 ± 169*</td>
</tr>
</tbody>
</table>

*0 = normal and 400 = brain death.
†p < 0.01 vs E, V, C and C.
E, endotracheal intubation; V, mechanical ventilation; C, chest compression.

Racemic pressures on the heart or intrathoracic vessels. There are potentially important clinical implications of these observations. In the absence of external ventilation during CPR, gasping is a life-sustaining response and remarkably effective. Approximately 60% of victims of out-of-hospital cardiac arrest experience gasping. The success of resuscitation has increased threefold for victims of sudden death who experience gasping.43

Mechanical Interventions

The primary goal of cardiac resuscitation during global myocardial ischemia of cardiac arrest is to reestablish myocardial blood flow so that spontaneous circulation may be restored. In 1960, the discovery by Kouwenhoven et al.10 that systemic, especially myocardial and cerebral, blood flow can be generated by external compression of the chest ushered in the modern era of CPR. External chest compression became the third priority of the ABCs and the standard of circulatory interventions.

One of the most important fruits of research on cardiac resuscitation during the past decade was the critical threshold of coronary perfusion for successful resuscitation. Standard techniques of external chest compression generate cardiac outputs less than 30% of normal. Coronary perfusion pressure and myocardial blood flow are correspondingly reduced.44 Accordingly, alternative methods of chest compression, including use of mechanical compression devices, have been tested. The intent is to increase both cardiac output and peripheral coronary and cerebral blood flows to more physiologic levels. These new interventions, all of which are still investigational, are modifications of conventional chest compression. In addition, invasive intravascular techniques have been investigated that operate in conjunction with chest compression. These contrast to open-chest cardiac compression, which continues to be an accepted and, indeed, essential option in instances of traumatic injuries to the chest, especially pericardial tamponade.
Mechanisms of Blood Flow During CPR

Blood flow is contingent on the driving force (i.e., pump) and vascular resistance. Most mechanical interventions for CPR focus on optimizing the driving force. However, there is little agreement on what constitutes an optimal driving force and the mechanism by which precordial compression acts as a driving force for forward blood flow. In fact, there is no agreement on how to measure this force.

Two distinct theories have been proposed, and each is supported by both experimental and clinical data (Fig. 2). The first is the cardiac pump mechanism originally postulated by Kouwenhoven et al. They assumed that the heart is compressed between the sternum and spine and that compression of the ventricles serves to eject blood into both the pulmonary and systemic circuits. In such settings, cardiac valve function would be preserved in a way that precludes back flow into the atria and veins and assures forward blood flow. There is evidence for this assumption. In addition, when compression is released, decreases in intrathoracic and intracardiac pressures are presumed to actively increase venous return and ventricular filling.

Under experimental conditions, precordial compression was followed...
by closure of the mitral valve and opening of the aortic valve. There were quantitatively appropriate pressure gradients among the atria, ventricles, and aorta during chest compression, which also were consistent with forward blood flow. More recent echo Doppler studies quite securely supported the observation that chest compression generates chamber deformation and appropriate valve function for forward blood flow. This serves as convincing evidence of a cardiac pump mechanism in experimental animals and in human victims.

These observations notwithstanding, there is also evidence based on animal and human data of a thoracic pump mechanism. Each precordial compression produces what initially appeared to be comparable increases in left and right ventricular pressures. Therefore, no effective pressure gradient for forward blood flow was identified. The proponents of the thoracic pump theory postulated that generalized increases in intrathoracic pressure were transmitted to the intrathoracic vasculature such that blood was extruded from the intrathoracic blood reservoir, including the heart and both large and small pulmonary blood vessels. This, rather than compression of the ventricles, was regarded as the mechanism that accounts for forward blood flow. Because patients who experienced ventricular fibrillation in the cardiac catheterization laboratory sustained forward blood flow by means of frequent and vigorous coughing, the so-called cough CPR emerged. This was interpreted as strong evidence in favor of the thoracic pump theory.

Proponents of the thoracic pump theory regarded the heart as a passive conduit. They further anticipated that both mitral and aortic valves remain open during chest compression. Valves between the intrathoracic and extrathoracic large veins were identified as barriers to backward flow. Forward blood flow was sustained by barriers against back flow provided by such venous valves. The claim that the heart was a passive conduit was consistent with observations on patients who underwent unsuccessful attempts at resuscitation. In terminal cardiac arrest states, especially after prolonged efforts failed to resuscitate either experimental animals or patients, valve function had stopped. The myocardium became less compliant, and a “stone heart” evolved. In this setting, the heart was indeed a passive conduit.

The consensus is that precordial compression produces increases in intrathoracic pressure and forward flow by means of a cardiac pump mechanism. The heart is compressed when increases in intrathoracic pressure are induced by means of external sternal compression, external circumferential compression, or “internal” compression in the instance of cough CPR. These forces are transmitted to the heart. The original concept that
cardiac compression is the result of direct compression of the heart between the sternum and the spine has not been sustained. During the early period of CPR, however, blood flow is generated by means of compression of the heart. The most recent study by Ma et al.50 confirmed that the heart becomes passive only after CPR is prolonged and that in such instances CPR fails to resuscitate the victim. When blood flow is generated by the thoracic pump under these conditions, mitral valve flow is less than one half of that generated during the period in which there is a cardiac pump.

**Monitors of the Efficacy of CPR**

The assumption that palpation of arterial pulses allows quantitation of the effectiveness of precordial compression for generating forward blood flow is currently not secured. This method of assessment was initially adopted by the American Heart Association.2 Palpation of either (or both) carotid and femoral pulses was cited as the only option for monitoring the effects of precordial compression on forward blood flow. It is now apparent, however, that arterial pulses at best represent only the palpable transmission of the pulsatile pressures generated during each chest compression. Peak arterial pressure has poor correlation with forward-flow cardiac output in patients, as is consistently demonstrated with direct intra-arterial pressure monitoring during precordial compression.

Our group investigated this issue on a porcine model. A balloon catheter was used that fully occluded blood flow at the level of the mid abdominal aorta. When the balloon was distended during precordial compression, the pressure pulse from the proximal aorta was very well transmitted to the aorta distal to the occluding balloon even though ultrasonic flow probes confirmed that there was no flow distal to the aortic occlusion. This demonstrated that pressure pulses are well transmitted in the absence of any flow during cardiac arrest. This contrasts to simultaneous measurement of aortic and right atrial pressures. The numerical difference between aortic diastolic and right atrial pressures serves as an estimate of coronary perfusion pressure. It represents a reliable indicator of myocardial perfusion during CPR.51-53 However, arterial and right atrial catheters are likely to be in situ in only a few patients who are being monitored, such as those in intensive care, operating room, or cardiac catheterization laboratory settings, at the time of cardiac arrest. Unfortunately, the complexity and time required for insertion of right atrial and aortic catheters during CPR preclude such monitoring for most victims. We therefore identify a critical need for measuring the effects of precordial compression or alternative methods for restoring circulation that can be rapidly implemented in the
CPR setting. Such techniques are now available. Measurement of end tidal \( \text{PCO}_2 \) and ECG ventricular fibrillation waveforms represent two options.

**Coronary Perfusion Pressure.** During spontaneous circulation, the resting coronary blood flow of human subjects averages about 230 ml/min, which is 0.7 to 0.8 ml/gm of heart muscle or 4% to 5% of total cardiac output. Coronary blood flow is regulated almost entirely by local arterial vasodilatation or vasoconstriction of the coronary arteries in response to myocardial oxygen requirements. During global myocardial ischemia of cardiac arrest, myocardial adenosine triphosphate (ATP) degrades to adenosine monophosphate (AMP) with release of adenosine. Adenosine produces maximal coronary vasodilatation. Myocardial blood flow then becomes essentially pressure dependent.\(^{53}\) Coronary blood flow is largely a diastolic event. In the CPR setting, compression diastole has a comparable function. The aortic diastolic pressure generated during chest compression is the primary determinant of coronary perfusion pressure.

The importance of threshold values of coronary perfusion pressure for successful resuscitation was initially recognized by Crile and Dolley in 1906. When cardiac arrest was induced in dogs by means of asphyxiation, successful resuscitation required coronary perfusion pressures of 30 mm Hg or greater. During the mid 1960s, Redding and Pearson also studied dogs during cardiac arrest. CPR was successful only when arterial diastolic pressure exceeded 40 mm Hg.\(^{54}\)

There are controversies regarding the definition of coronary perfusion pressure during CPR. Most experts define coronary perfusion pressure as the difference between mean aortic and right atrial diastolic pressures; others define it as peak diastolic pressure, and a third group uses mid-diastolic pressures.\(^{51,55}\) Nevertheless, there is almost unanimous agreement that each of these measurements is highly correlated with myocardial blood flow, and as such coronary perfusion pressure serves as a reliable prognostic factor. The minimal coronary perfusion pressure of 15 to 20 mm Hg is a predictor of successful resuscitation for human victims provided that CPR is initiated less than 5 minutes after the onset of cardiac arrest. Substantially greater coronary perfusion pressures are required for restoration of spontaneous circulation among victims for whom CPR is delayed more than 5 minutes.\(^{44}\)

The critical level of coronary perfusion pressure is 15 mm Hg. Unless this threshold is reached, the likelihood of resuscitation is remote. Increases in coronary perfusion pressure account for proportionately greater survival. When coronary perfusion pressure was greater than 24 mm Hg in one study, more than 70% of patients underwent successful resuscitation (Fig. 3).\(^{24}\) These observations notwithstanding, coronary perfusion pres-

ure is predictive only of the likelihood of successful resuscitation and not necessarily ultimate (hospital) survival.

**End Tidal PCO₂** Initial studies on animals and subsequent observations of patients demonstrated marked increases in the PCO₂ of mixed venous blood during CPR. There were even greater increases in the gradient of PCO₂ between mixed venous blood and arterial blood. These effects on mixed venous and arterial blood were traced to proportionate reductions in cardiac output and therefore in pulmonary blood flow during CPR. Changes in end tidal PCO₂ (P_{ET}CO₂) during CPR correlated with the cardiac output of animals and in patients. P_{ET}CO₂ was therefore identified as a good quantitative monitor of blood flow generated during CPR.

In our review of the literature, we learned that the concept of measuring P_{ET}CO₂ was not original with our group. In 1939, Eisenmenger²⁸ had referred to expired CO₂ as an indicator of blood flow generated by a Biomotor, which he designed as a compressor of the chest and abdomen during cardiac arrest. In 1978, Kalenda and Smallhout²⁹ published capnographs indicating the potential value of measurement of expired CO₂ for guiding CPR and specifically for identifying the onset of fatigue of the operator. Both decreases in P_{ET}CO₂ and concurrent decreases in the frequency of chest compressions signaled a decline in forward blood flow generated during CPR. Sanders et al.⁶⁰ independently demonstrated a high correlation between P_{ET}CO₂ and coronary perfusion pressure during both closed- and open-chest CPR in a study with dogs. These studies provided additional confirmation that P_{ET}CO₂ is a useful monitor. It has the additional and im-

important advantage of being noninvasive. It also represents a continuous measurement and therefore a moment to moment monitor of the hemodynamic response to CPR. P<sub>ET</sub>CO<sub>2</sub>, like coronary perfusion pressure, correlates with the outcome of CPR and therefore also serves as a prognostic indicator in the treatment of patients.

A P<sub>ET</sub>CO<sub>2</sub> less than 10 mm Hg was a predictor of failure in each of 26 trials with patients (Fig. 4).<sup>61</sup> An initial P<sub>ET</sub>CO<sub>2</sub> of 15 mm Hg or greater allowed prediction of successful CPR.<sup>61,62</sup> P<sub>ET</sub>CO<sub>2</sub> may be affected by the volume and frequency of ventilation, although this is unlikely to be important at tidal volumes of approximately 10 ml/kg and frequencies of 12 breaths/min. Pulmonary ventilation-perfusion ratios such as those associated with pulmonary emboli also may decrease P<sub>ET</sub>CO<sub>2</sub> but to levels of 20 to 25 mm Hg rather than to threshold values except in settings of circulatory shock. More important, bicarbonate buffering agents transiently increase P<sub>ET</sub>CO<sub>2</sub>, and the organic buffering agent tromethamine decreases P<sub>ET</sub>CO<sub>2</sub>.

**Ventricular Fibrillation Amplitude and Frequency.** Ventricular fibrillation (VF) amplitude serves as a predictor of the outcome of CPR. Both outcome of the CPR attempts and hospital survival rates have been correlated with VF amplitude (Fig. 5). Retrospective studies showed that VF amplitude served as a powerful indicator of outcome after cardiac arrest.<sup>63</sup>

Our group performed prospective studies, including a study of the relation between coronary perfusion pressure and VF amplitude. Considerably greater coronary perfusion pressure and VF amplitude (Fig. 6) were

FIG. 6. Representative analog record of electrocardiogram during cardiopulmonary resuscitation of a rat that was resuscitated and a rat that failed resuscitation attempts. Recordings were obtained after 4 minutes of cardiac arrest. BL, baseline; PR, postresuscitation.

observed among successfully resuscitated animals. The increases in VF amplitude during CPR indicated reversal of hypoxia. Increases in myocardial creatine phosphate and decreases in myocardial lactate concentration were demonstrated. These indications of the potential value of VF am-
Fig. 7. Prediction of successful resuscitation based on maximal peak to trough ventricular fibrillation amplitude (MAX AMPL), mean peak to trough ventricular fibrillation amplitude (MEAN AMPL), and dominant frequency of ventricular fibrillation (D-FREQ) during precordial compression before defibrillation (*p < 0.001). R, resuscitated, NR, nonresuscitated.

Atmosphere provoked substantial interest in not only mean and maximal VF amplitude but also in the dominant VF frequency. Each of the three parameters served as predictors of outcome (Fig. 7). These findings added strong experimental foundations for the use of VF waveforms to monitor interventions and predict outcomes during CPR.

Chest Compression

Conventional Precordial Compression. The standard technique of external precordial compression has changed little since it was popularized in the landmark paper of Kouwenhoven et al. in 1960. External chest compressions are applied by a rescuer, who places the heel of one hand over the lower half of the victim’s sternum and the other hand on top of the first hand. The downward force compresses the sternum to the extent that the anteroposterior chest thickness of an adult is decreased by 3.5 to 5.0 cm.

The hemodynamic efficacy of precordial compression depends largely on the force, rate, and duration of chest compression. Mechanical compression devices, especially the Michigan Thumper (Michigan Instruments, Grand Rapids, Mich.) give the advantage of consistency without operator fatigue. However, use of these devices does not give greater benefit than optimal manual compressions. Devices are useful during transport and in closed spaces like elevators in which access to the victim by rescuers is restrained.
Vigorous chest compression produces a marked increase in forward blood flow, even though there is risk of traumatic injuries. When the rate of chest compressions is doubled, coronary perfusion pressure, initial resuscitation, likelihood of 24-hour survival, and neurologic recovery all increase markedly. Cardiac output and coronary perfusion pressure also increase when the duration of compression is prolonged to represent as much as one half of the total compression relaxation cycle.

The hemodynamic efficacy of precordial compression progressively decreases with increasing duration of the resuscitation effort. This is best explained by decreases in myocardial compliance and chest wall compliance. It is for this reason that greater increases in thoracic pressure are required to generate the same cardiac output. Ischemia and its effect on reducing myocardial compliance was reviewed earlier. Chest compliance decreases after repetitive compressions deform the bony thorax and cause rib fractures. Accordingly, precordial compression is maximally effective during the initial 5 minutes of CPR. After 30 minutes, efficacy of chest compression is reduced to the extent that forward flow is unlikely to be adequate for successful resuscitation.

Operator fatigue has emerged as an important variable. It accounts for decreases in effective forward flow produced by precordial compression. Both thoracic and abdominal structures are injured by chest compression among as many as 60% of victims. Ribs are fractured most frequently and sometimes the sternum. The sternum is rarely implicated in direct injury to the viscera. However, the blunt force of chest compression produces variable injuries to the heart, great vessels, pleura and lungs, and the liver. At autopsy, these account for pulmonary edema, hemothorax, pneumothorax, and hemoperitoneum.

**Interposed Abdominal Compression.** In 1976, Ohomoto et al. proposed that in tandem with precordial compression, the abdomen be intermittently compressed. Abdominal compression was programmed for the relaxation intervals between chest compressions. A force intended to be equivalent to 200 mm Hg was applied by a second rescuer at a site equidistant from the xiphoid process and the umbilicus (Fig. 8). The effects of interposed abdominal compression were investigated by Sack et al. on patients in the hospital. With the use of interposed abdominal compression, the initial resuscitation rate was doubled and the hospital discharge rate increased more than four times compared with conventional precordial compression. Greater efficacy of interposed abdominal compression was explained by a combination of three mechanisms: augmented intrathoracic pressure; compression of the abdominal aorta to impede infradiaphragmatic runoff of aortic blood flow during compression dias-
FIG. 8. Interposed abdominal compression. The arrows indicate the sequence of chest and abdominal compression and relaxation.

to; and augmentation of venous return to the right atrium by means of compression of abdominal viscera. Two follow-up studies by independent investigators included a total of 154 out-of-hospital victims; however, neither of these follow-up studies demonstrated increases in coronary perfusion pressure or improved outcome compared with conventional CPR. 58,69

Vest Cardiopulmonary Resuscitation. The concept of circumferential chest compression was developed by cardiopulmonary researchers at Johns Hopkins University in the mid 1980s. A vest was constructed much like that of a very large blood pressure cuff (Fig. 9). The vest was programmed to inflate and deflate 60 times per minute. A maximum pressure of 250 mm Hg was applied to the thorax with a pneumatic pump. In experiments on dogs subjected to ventricular fibrillation, this technique maintained greater myocardial and cerebral blood flows than conventional precordial compression. An increase in 24-hour survival rate was statistically significant. 70 However, no statistically significant increases in coronary perfusion pressure or improvement in outcome were observed in out-of-hospital settings with human victims. 71 After the size of the vest and the pressure applied circumferentially were increased, greater peak aortic pressures and coronary perfusion pressures were obtained. As yet, no significant increase in resuscitation or 24-hour survival on human victims has been confirmed. 72 Nevertheless, there is substantial optimism about the procedure; a comprehensive clinical trial of vest CPR is in process.
The mechanisms by which vest CPR was intended to increase hemodynamic efficacy are as follows. First, the compression force and consequent intrathoracic pressure are greater than those achieved with conventional methods. Because compression forces are evenly applied circumferentially around the chest, the increases in intrathoracic pressure are substantially increased with lesser decreases in intrathoracic volume. Second, expiratory airflow is decreased and intrathoracic pressure is augmented. In theory, traumatic injury would be minimized because compression forces are distributed circumferentially over a much larger area. Only incomplete data from trials involving human subjects are available but eagerly awaited. If the incidences of traumatic injuries are less than those obtained with conventional precordial compression, it would be an important asset.

Active Chest Compression-Decompression. According to Lurie et al., active chest compression-decompression was first suggested in a case report in which a 65-year-old victim of sudden death was resuscitated by his son with a toilet plunger. The device developed for experimental trials consisted of a manually operated plunger, not unlike that of the rubber part of a conventional toilet plunger. It was applied to the precordium with a suction cup that allowed active lifting of the anterior chest wall after chest compression (Fig. 10). The following theoretic assumptions prompted the trials. First, active decompression produces greater chest expansion and therefore larger differences in intrathoracic pressure between compression and decompression than does conventional compression and would be likely to generate greater forward blood flow. Second, chest decompression provides negative intrathoracic pressure with consequent increases in venous return. Third, the pressure gradient between the aorta and the

FIG. 9. Device for vest cardiopulmonary resuscitation. The vest, which is similar to a large blood pressure cuff, provides circumferential compression of the chest.
right atrium favors uninterrupted coronary perfusion during both chest compression and relaxation.

In experiments, active compression-decompression was associated with a statistically significant increase in myocardial, cerebral, and renal blood flow, coronary perfusion pressure, rate of initial resuscitation, and 24-hour survival rate compared with conventional precordial compression.\textsuperscript{74,75} In two randomized clinical studies that included a total of 115 patients after in-hospital cardiac arrest, active compression-decompression essentially doubled the success rate of initial resuscitation and tripled 24-hour survival rate compared with conventional precordial compression. Unfortunately, there were no statistically significant increases in ultimate hospital survival rate.\textsuperscript{76,77}

Three additional randomized studies were performed. In one that involved 130 victims, initial resuscitation rate increased, but there were no statistically significant increases in the number of hospital survivors.\textsuperscript{78} Another study with 860 victims\textsuperscript{79} and a third with 1784 victims\textsuperscript{80} did not demonstrate any benefit over conventional precordial compression with respect to return of spontaneous circulation, survival until hospital admission, hospital survival, or neurologic recovery.

The only optimistic report on victims of out-of-hospital cardiac arrest who were randomized to protocols of either active compression-decompression or conventional precordial compression was by Plaisance et al.\textsuperscript{81} with 512 victims. There was significantly greater initial success of resuscitation, 24-hour survival, and hospital discharge with active compression-decompression. The authors, however, reported that the improvement in number of hospital survivors was small, 14 as opposed to five patients. The investigators attributed the apparently better outcomes to provision of better training, collaboration between emergency medical...
technician and physician providers, and sufficient personnel that fatigue of the individual rescuer was minimized. In addition, the pressure values that corresponded to maximal compression and decompression were quantitatively displayed to the rescuers and therefore the quality of the intervention was controlled.

Except for greater injury to the skin, the adverse effects of active compression-decompression are comparable with those of conventional precordial compression. There are isolated case reports of spleen and liver injuries associated with active compression-decompression, especially among patients who underwent previous surgical exploration of the abdomen.

**Phased Chest and Abdominal Compression-Decompression.** Phased chest and abdominal compression-decompression is the newest alternative. It incorporates chest compression-decompression and abdominal compression. Experimental outcomes were reported only weeks before the completion of this article. A manually operated Lifestick resuscitator (Datascpe, Fairfield, N.J.) is used. The chest and abdomen are reciprocally compressed and decompressed in a seesaw manner. The method is illustrated in Fig. 11. The device is designed so that the precordium is compressed with a force of 120 pounds (54 kg) and the abdomen with a force of 50 pounds (22.5 kg). Conventional chest compression produces a force of 160 pounds (72 kg). Compression is at a rate of 60 cycles/min, and both the angles and phases of compression and decompression are optimized.

This technique combines the advantages of both active chest compression and decompression and abdominal compression and introduces the concept of abdominal decompression. Abdominal decompression is intended to reduce both left and right ventricular afterloads. Such would favor better stroke volumes during chest compression. Experimental studies demonstrated impressive hemodynamic efficacy. The coronary perfusion pressure generated with the Lifestick resuscitator was threefold greater than that generated with conventional precordial compression. This was associated with striking improvement in initial capability for resuscitation and 72-hour survival rate. Hemodynamic efficacy was demonstrated in early trials with human subjects. Among 10 out-of-hospital victims of cardiac arrest, the coronary perfusion pressure generated with the Lifestick resuscitator was more than fourfold greater than that obtained with conventional precordial compression. More comprehensive proof of efficacy and data on complications for human victims is awaited. Experimental studies indicated that the Lifestick resuscitator markedly improves efficiency and achieves greater forward flow with lower compression force.
than conventional compression. This would explain statistically significantly fewer instances of rib fractures and injuries to the thoracic contents during trials on pigs.

**Intravascular Methods**

*Aortic Balloon Occlusion*. A new option for CPR by use of intermittent occlusion of the ascending aorta was introduced by our group in 1993. The technique involves use of a balloon catheter advanced into the ascenden-
ing aorta (Fig. 12). The balloon is inflated for 30 seconds during each minute of precordial compression. When the ascending aorta is occluded by a balloon proximal to the innominate artery, the entire cardiac output generated by precordial compression is directed into the coronary circuit. Coronary blood flow increases dramatically. Coronary perfusion pressure typically increases from 12 mm Hg to more than 90 mm Hg. Even though cerebral blood flow is stopped for 30 seconds of each minute, no neurologic deficit was identified in experimental animals. The success of initial resuscitation attempts and 48-hour survival rate after successful resuscitation of pigs was impressive.

Other researchers have used occlusion of the thoracic descending aorta at a site comparable with that used for balloon counterpulsation. Placement of the balloon catheter was therefore accomplished with ease. The hemodynamic efficacy of aortic occlusion at this more distal site was smaller than with occlusion of the ascending aorta. As yet, no experience with balloon occlusion in the treatment of patients has been reported. Both operator skill and the time required for insertion of the balloon catheter under the crisis conditions of CPR are likely to be formidable constraints.

**Extracorporeal Circulation.** Although technically demanding, extracorporeal circulation is the most hemodynamically effective intervention for cardiac resuscitation. However, it requires even more skill and involves greater complexity of instrumentation than balloon occlusion. Both arterial and venous cannulas are required, typically in-
serted by means of percutaneous or surgical cannulation. The femoral artery and vein are utilized together with anticoagulation, extracorporeal pump oxygenation, and priming fluids. After extracorporeal circulation has been established, coronary perfusion pressure is almost immediately increased to physiologic levels. If used in a timely manner to treat victims when conventional methods fail, extracorporeal circulation allows successful restoration of spontaneous circulation, even after 20 minutes of untreated cardiac arrest. The technique is necessarily confined to patients who sustain cardiac arrest in the hospital, especially in catheterization laboratories, coronary care units, operating rooms, and emergency departments.

A key advantage of extracorporeal circulation is that it provides a respite during which emergency diagnostic procedures can be completed and definitive intervention can be planned and potentially exercised. Hill et al. used extracorporeal circulation for the resuscitation of cardiac arrest victims in 17 institutions and on 125 patients. Conventional CPR had failed in each instance. Extracorporeal circulation was successfully established in more than 75% of instances. Mean aortic pressure was greater than 60 mm Hg and systemic blood flow greater than 2 L/m² in these instances. Spontaneous circulation was restored for 20% of the patients, more than two thirds of whom lived at least 30 days. When extracorporeal circulation was initiated within 15 minutes, 35% of patients were resuscitated. Patients with refractory cardiac arrest after more than 30 minutes of conventional CPR were poor candidates for extracorporeal circulation therapy. Complications include bleeding and vascular injury resulting from rapid cannulation.

Open-Chest Cardiac Massage

Open-chest cardiac massage was initially used more than 120 years ago. Direct manual compression of the heart represented the primary in-hospital intervention during the 1940s and 1950s. The reported survival rate was an impressive 28%. Patients were successfully restored to spontaneous circulation after as long as 20 minutes of untreated cardiac arrest. In the 1960s, however, external precordial compression replaced surgical thoracotomy and open-chest cardiac massage. Precordial compression came into routine use because of its universal applicability by nonphysician providers and potentially by the general public. Open-chest cardiac massage is now used only in settings of cardiac arrest after penetrating chest trauma, after surgical thoracotomy, or when bony deformities of the chest preclude successful chest compression.

An anterolateral thoracotomy is typically performed through the fifth
intercostal space. The ribs are mechanically spread apart. The medical
rescuer's open right hand with the palm facing anteriorly is advanced pos-
teriorly behind the left ventricle for compression of the heart anteriorly
against the posterior surface of the sternum. Compressions are at a rate of
60 per minute. After each compression, the operator's hand is released
completely to allow for diastolic filling of the ventricles.

Open-chest cardiac massage is unequivocally more effective than exter-
nal chest compression. In studies on dogs, it produced much greater coro-
nary perfusion pressure (58 mm Hg vs 20 mm Hg), success of initial re-
suscitation (100% vs 20%), and 7-day survival (79% vs 29%) than external
compression.\textsuperscript{88,89} In clinical settings, open-chest cardiac massage also gen-
erates greater cardiac output and increases likelihood of initial resuscita-
tion and survival. However, ultimate outcomes, especially in settings of
out-of-hospital cardiac arrest, have not improved.\textsuperscript{90} The much greater in-
vasiveness of open-chest cardiac massage carries a greater incidence of
complications, including traumatic injuries to the heart, lungs, and sur-
rounding soft tissues. Infection is a lesser issue.

\textit{Incorporation of Newer Methods into Clinical Practice}

There is as yet no statistically secure documentation that any of the newer
closed-chest or even open-chest options have improved functional sur-
vival in clinical settings. We express some optimism about phased-chest
and abdominal compression-decompression but without proof. For the
present, conventional chest compression by means of either manual or
mechanical methods remains the only option of proved effectiveness
except for traumatic injuries, for which open-chest methods are usually
mandatory.

Of signal importance with respect to the success of resuscitation and
ultimate survival is the duration of untreated cardiac arrest before the in-
tervention. The more prolonged the cardiac arrest, the less is the hemody-
namic efficacy of the mechanical intervention for restoring blood flow.
Except for extracorporeal circulation, each of the new techniques incorpo-
rates one or more modifications of conventional precordial compression.
All depend on the arresting heart to generate cardiac output.

Largely unexplored are the dynamic changes in left ventricular volume
and compliance during cardiac arrest and CPR. During global ischemia of
cardiac arrest, the heart muscle is impaired. The heart loses compliance
and ultimately becomes a "stone heart."\textsuperscript{91} This decreases the efficacy of
compression. After coronary blood flow is restored, so-called reperfusion
injury may preclude effective myocardial contractility and usher in
postresuscitation myocardial dysfunction.
Pharmacologic Interventions

During CPR, blood flow is determined primarily by two factors—the pump (driving force) and peripheral vascular resistance. Mechanical interventions are intended to generate maximal cardiac output and perfusion pressures. A second issue is vascular tone. Accumulation of metabolic vasodilator substances, including adenosine, carbon dioxide, lactic acid, and hydrogen ions, and lesser neurovascular vasoconstrictor activity are implicated in the decreases in peripheral arterial resistance due to arterial vasodilatation. In addition, variable increases in venous capacitance reduce venous return to the right atrium. This has been the basis for routine efforts to use vasopressor agents, especially α-adrenergic agents, to restore spontaneous circulation.

Pharmacologic interventions during CPR are restrained by (1) impaired distribution of drugs or their metabolites such that they are incapable of acting on their targets and (2) changes in the pharmacologic actions of the drugs by acidosis, hypercarbia, hypoxemia, down regulation of receptors, and altered organ function. Drug metabolism also is altered in the nonflow or low-flow setting of CPR. Inadequate clinical history of underlying diseases and concurrent drug treatment further thwart precision of pharmacologic interventions. For practical purposes, the mainstay of pharmacologic management, other than management of underlying causes, involves the use of vasopressor agents and no other drugs.

Mechanisms of Adrenergic Agents

The primary effect of adrenergic agonists is to activate adrenergic receptors. In 1948, Ahlquist first hypothesized that catecholamines acted through two principal receptors. He called these receptors α and β. This hypothesis was proved to be both correct and useful.\textsuperscript{92} Drugs were developed that served as either α or β agonists or antagonists. In the years that followed, additional α- and β-receptors were identified. α-Adrenergic receptors were classified into two subgroups. α\textsubscript{1}-Receptors (presynaptic α-receptors) were identified in the heart and vascular and intestinal smooth muscle. α\textsubscript{2}-Receptors (postsynaptic α-receptors) were present in vascular smooth muscle, pancreatic islets (β cells) and platelets. The α\textsubscript{1}-receptors have been further subcategorized into α\textsubscript{1A}, α\textsubscript{1B}, and α\textsubscript{1D} receptors and the α\textsubscript{2}-receptors into α\textsubscript{2A}, α\textsubscript{2B}, and α\textsubscript{2C} adrenergic receptors.\textsuperscript{92,93} At the time of this writing, individual functions of these subtypes with respect to cardiac resuscitation have not been established. β\textsubscript{1}-Receptors were identified primarily in the heart. β\textsubscript{2}-Receptors were localized in vascular and bronchial smooth muscle and skeletal muscle. A β\textsubscript{3}-receptor was identified in adipose tissue.\textsuperscript{94}
Activation of α-adrenergic receptors is followed by release of intracellular Ca^{2+} from endoplasmic stores, activation of G protein-gated K^+ channels, and inhibition of voltage-sensitive calcium channels. These increase intracellular availability of Ca^{2+} and consequent contraction of vascular smooth muscle. The number of active adrenergic receptors may be increased during global myocardial ischemia and exert arrhythmogenic actions on the myocardium.

Both β_1 and β_2 agonists activate adenylate cyclase and convert ATP to cyclic adenosine monophosphate (cAMP). This is the so-called second messenger that activates protein kinase and voltage-sensitive calcium channels. In the heart, they induce inotropic and chronotropic effects with increases in myocardial oxygen consumption. In vascular smooth muscle, they induce relaxation and reduced peripheral vascular resistance. Cardiovascular effects of β_2-receptors have not been fully defined.

**Routes of Administration**

The route of drug administration is selected to assure rapid and complete distribution and early pharmacologic action. Intravenous injection secures such and also assures better predictability of blood (plasma) concentrations. Use of alternative routes, especially endotracheal administration, is less predictable with respect to absorption, distribution, and pharmacologic response; it is limited to settings in which intravenous routes cannot be readily accessed.

**Intravenous Route.** Peripheral venous access has the advantages of minimal invasiveness, technical ease, and physical access. However, the pharmacologic responses and the peak blood concentrations of the drugs are more predictable after central venous injection or infusion. In the experiments by Emerman et al. the circulation time of a dye tracer after central venous injection was 63 seconds; in peripheral venous injection it was 94 seconds. The peak dye concentration after central venous injection was also statistically significantly greater. Central venous access may be facilitated through the femoral vein. The internal jugular vein and subclavian vein are appropriate alternatives but are likely to compromise CPR intervention, including both chest compression and airway management. Local complications of venous cannulation, including hematoma, cellulitis, thrombosis and phlebitis, and systemic complications, including sepsis and pulmonary thromboembolism, are of little importance in the CPR setting. Air embolism is best avoided with jugular or subclavian cannulation by means of maintaining the patient in a 10% head-down posture.

**Endotracheal Route.** When an endotracheal tube is in place, pharmacologic agents can be delivered as much as 4 minutes earlier by way of the
endotracheal route. In such settings, endotracheal administration has advantages, more so for children, obese victims, and victims of cardiac arrest due to drug abuse, for whom venous access may be difficult. The pulmonary circulation receives the totality of the cardiac output, and the lungs provide approximately 70 m² capillary surface for drug absorption. A prolonged pressor effect of epinephrine, the so-called depot-like effect, of up to 30 minutes' duration follows endotracheal administration. Intravenous injection produces pressor effects of 3 to 5 minutes' duration. Tachycardia, hypertension, dysrhythmias, and lower fibrillation threshold may be encountered after successful resuscitation after endotracheal injection. Therefore only a single dose of epinephrine should be administered by way of the endotracheal route. No drug other than epinephrine is recommended for endotracheal administration during CPR. The dose may be increased to 3 mg diluted in 10 ml of either normal saline solution or sterile water. Injection is best followed by two or three forceful lung inflations. Complications are minimal. Only a minor and transient decrease in arterial PO₂ and increased arterial PCO₂ may be observed.

**Effects of Adrenergic Agents During CPR**

The universal use of epinephrine as a vasopressor drug is being challenged. The β₁ effects of epinephrine account for large increases in myocardial oxygen consumption. Myocardial ischemia is likely to be identified in settings of CPR, increasing the severity of postresuscitation myocardial dysfunction. This may explain, at least in part, the disappointing outcomes after resuscitation that include injection of epinephrine, especially in the setting of out-of-hospital cardiac arrest. During CPR, adrenergic agents with predominant α₁ effect have been shown to be more effective as vasoconstrictor drugs, presumably because extrajunctional α₂-receptors are more accessible to circulating catecholamines than postjunctional α₁-receptors. This may explain why adrenergic amines that have predominant α₁ actions such as methoxamine (Vasoxy) and phenylephrine (Neo-Synephrine) are less effective than epinephrine after prolonged cardiac arrest.

**Epinephrine.** Epinephrine has been the preferred adrenergic agent for the treatment of patients with cardiac arrest for more than 35 years. There is persuasive evidence that its efficacy is due to its α-adrenergic vasopressor effects. More recently, the potentially adverse effects of epinephrine are related to its inotropic actions that provoke disproportionate increases in myocardial oxygen consumption. Epinephrine thereby increases the severity of global myocardial ischemic injury during cardiac arrest. Equally important, it intensifies postresuscitation myocardial dysfunction. Despite
such factors, epinephrine is the drug of first choice in the management of cardiac arrest at the time of this writing.

Epinephrine is a powerful agonist of $\alpha_1$, $\alpha_2$, $\beta_1$, and $\beta_2$-adrenergic receptors, and its pharmacologic effects are correspondingly complex. Primary effects on the myocardium are the $\beta_1$ actions, which are both inotropic and chronotropic. During ventricular fibrillation, the contractile force of the fibrillatory segments is increased, and this accounts for the increases in myocardial oxygen consumption even though the heart is not doing any effective work. Postresuscitation myocardial dysfunction is best explained by the increases in myocardial ischemic injury provoked by epinephrine during CPR. The $\beta$-adrenergic effects of epinephrine also account for greater incidence of postresuscitation ventricular dysrhythmias, tachycardia, and fibrillation in close relation to its chronotropic actions. Increases in ventricular fibrillation voltage reflect $\alpha$-adrenergically induced increases in coronary blood flow. This is now known to allow more effective defibrillation with lesser electrical power.

Epinephrine induces disproportionate increases in systolic pressure. Accordingly, the pulse pressure is increased. The effect of epinephrine on small arterioles and precapillary sphincters accounts for altered blood flow distribution to tissues and organs. Cutaneous and renal vasoconstriction is marked and accounts for the reduced blood flow to these sites. However, neither cerebral nor coronary arterioles are constricted. Cerebral and coronary blood flows are disproportionately increased at the expense of cutaneous and renal blood flows. High-dose epinephrine may increase pulmonary artery, pulmonary capillary, and pulmonary venous pressures. The resulting increases in pulmonary capillary filtration pressure may precipitate pulmonary edema. For the same reasons, pulmonary ventilation-perfusion defects appear, and these are characterized by pulmonary arteriovenous admixture with decreases in $P_{\text{aO}_2}$, increases in $P_{\text{aCO}_2}$, and decreases in end-tidal $P_{\text{CO}_2}$. The $\beta_2$ actions of epinephrine are predominantly bronchodilator effects, and these have no recognized beneficial or adverse effects during CPR.

Although epinephrine has been recommended by the American Heart Association as the drug of choice for CPR since 1974, there is as yet no confirmation that ultimate outcomes are improved, either in settings of in-hospital or out-of-hospital cardiac arrest. A placebo-controlled clinical study is both ethically and legally problematic. Nevertheless, until well designed clinical studies indicate otherwise, we recommend that epinephrine be restricted to treatment of victims of cardiac arrest who do not respond to initial basic life support and prompt electrical defibrillation.

The optimal dose of epinephrine for the treatment of cardiac arrest was
TABLE 3. The effect of adrenergic agents on outcomes of cardiopulmonary resuscitation

<table>
<thead>
<tr>
<th>Group</th>
<th>No. resuscitated</th>
<th>Survival time (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>5/5</td>
<td>7 ± 5</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>5/5</td>
<td>38 ± 14*†</td>
</tr>
<tr>
<td>Epinephrine &amp; esmolol</td>
<td>5/5</td>
<td>30 ± 10*†</td>
</tr>
<tr>
<td>Saline placebo</td>
<td>3/5</td>
<td>3 ± 1</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
* p < 0.01 versus epinephrine.
† p < 0.01 versus saline.

not addressed until 1974 when the Guidelines and Standards of the American Heart Association specified bolus injection of 0.5 to 1.0 mg independent of weight. In 1985, Ralston et al. reported that higher doses of epinephrine, 0.01 to 0.1 mg/kg, improved the resuscitation rate from 40% to 90%. A series of studies addressed the role of “high-dose” epinephrine. Both experimental studies and clinical reports confirmed that high doses of epinephrine produced greater coronary perfusion pressure, myocardial and cerebral blood flow, and rate of initial resuscitation. Nevertheless, there was no proof of greater long-term survival rates. These reports triggered three large, randomized clinical studies that included documentation of benefits of ultimate survival based on tallies of neurologically intact hospital survival. The studies compared standard and high doses of epinephrine in the setting of either out-of-hospital or in-hospital cardiac arrest. There was a trend but no statistically significant improvement in the rate of initial resuscitations with high-dose epinephrine. Most important, however, was the failure to confirm statistically significant differences in initial rate of resuscitation, neurologic outcome, and hospital discharge. The most recent American Heart Association Guidelines for Advanced Cardiac Life Support confirm 1 mg of intravenously injected epinephrine as the appropriate initial dose. The use of high doses of epinephrine is regarded as potentially helpful in some settings but not recommended at this time.

The main adverse effect of administration of epinephrine during CPR is to increase the severity of myocardial ischemic injury by its $\beta_1$ effects, which adversely affect postresuscitation myocardial function and survival. Epinephrine increases myocardial lactate concentration and decreases myocardial ATP content even though coronary blood flow may be doubled. Epinephrine increases the severity of postresuscitation myocardial dysfunction and decreases postresuscitation survival compared with the selective $\alpha$-agonist phenylephrine. After epinephrine was combined with the $\beta_1$-blocking agent esmolol (Table 3), the effects were compa-
rable with those of phenylephrine. Epinephrine increased the incidence of ventricular arrhythmias, ventricular tachycardia, and (recurrent) ventricular fibrillation. There was a statistically significant decrease in these ventricular arrhythmias after β-adrenergic blockade. When patients are resuscitated after a relatively short duration of CPR, a brief period of epinephrine-induced hypertension may occur; this increases afterload and further decreases cardiac output. The β-adrenergic actions of epinephrine increase the severity of myocardial ischemic injury and thereby the likelihood of reentrant and ectopic ventricular dysrhythmias.

**Norepinephrine.** Norepinephrine is the main mediator of mammalian postganglionic adrenergic function. Its chemical structure is identical to that of epinephrine except that it lacks methyl substitution in the amino group of the phenylethylamine nucleus. Between 10% and 20% of the catecholamine content of the adrenal medulla of persons is composed of norepinephrine. Norepinephrine is a potent α-adrenergic agonist that stimulates both α₁- and α₂-receptors. It has only minor β₂-receptor actions. Like epinephrine, norepinephrine also acts on β₁-receptors and increases myocardial oxygen consumption and risk for ischemic injury during CPR. In contrast to epinephrine, it produces greater arterial constriction such that total peripheral resistance is markedly increased. Both arterial systolic and diastolic pressures are increased with more narrow pulse pressure. Blood flow to skeletal muscle, liver, and kidneys is markedly decreased. Like epinephrine, norepinephrine produces coronary artery dilatation and together with increases in arterial blood pressure augments coronary blood flow. The circulating blood volume is reduced after administration of norepinephrine, primarily as a consequence of peripheral vascular constriction. Capillary hydrostatic pressure is increased, resulting in filtration of protein-free fluid into the extracellular compartment. Both myocardial and cerebral blood flow are increased, comparable with the increase caused by epinephrine. The main difference is in myocardial oxygen consumption. It is considerably less after administration of norepinephrine.¹⁰⁶,¹⁰⁷

In a randomized study with 50 persons who sustained cardiac arrest outside a hospital, Lindner et al.¹⁰⁸ compared the effect of equal doses of norepinephrine and epinephrine during CPR. The initial rate of successful resuscitation was statistically significantly greater for the norepinephrine group than for the epinephrine group. No statistically significant increase in the number of survivors neurologically intact at hospital discharge was detected. In a larger randomized study with 816 victims of out-of-hospital cardiac arrest, Callaham et al.¹⁰⁰ found no statistically significant differences between norepinephrine and epinephrine groups with respect to initial success of resuscitation and hospital survival. There are no convincing
data to support the routine use of norepinephrine as an alternative to epinephrine in settings of cardiac resuscitation at the time of this writing.

**Methoxamine.** Methoxamine is a relatively pure $\alpha_1$-adrenergic agonist. It blocks $\beta$-adrenergic receptors at high doses. The predominant cardiovascular effect of methoxamine is to increase peripheral vascular resistance. Under physiologic conditions, methoxamine induces sinus bradycardia by means of activation of vagal reflexes. Methoxamine has been a vasopressor agent of special interest in CPR since the 1960s. Redding and Pearson$^{109}$ compared the effects of methoxamine with those of epinephrine in the setting of ventricular fibrillation due to asphyxiation. Methoxamine yielded substantially better initial resuscitation with return of spontaneous circulation. Roberts et al.$^{110}$ compared the effects of methoxamine and epinephrine on myocardial and cerebral blood flows during CPR. Methoxamine yielded greater myocardial and cerebral blood flows during precordial compression. Postresuscitation cardiac output and survival were greater than that obtained with epinephrine. These observations differed from those of Brown et al.$^{111}$ who reported that myocardial blood flow was greater with epinephrine than with methoxamine. Differences between observations may be explained by the rapid down regulation of presynaptic $\alpha_1$-adrenergic receptors during cardiac arrest. Vasomotor tone is then maintained by postsynaptic $\alpha_2$-adrenergic receptors. Whereas the first dose of methoxamine was administered by Roberts et al. after 3 minutes of cardiac arrest, Brown et al. waited for 10 minutes.

In a prospective, randomized, double-blind study involving 80 persons who sustained out-of-hospital cardiac arrest with electromechanical dissociation, Turner et al.$^{112}$ compared the effects of 1 mg of epinephrine and 10 mg of methoxamine on both initial success of resuscitation and hospital discharge rate. No statistically significant differences in outcomes were observed. There also were no differences in outcomes between the two drugs when they were used for patients with out-of-hospital ventricular fibrillation.$^{113}$ The evidence favors neither the routine use of epinephrine over methoxamine nor the use of methoxamine over epinephrine.

**Phenytoin.** Phenytoin is an $\alpha_1$-adrenergic agonist. Unlike methoxamine, however, it is a weak activator of $\beta$-adrenergic receptors. The pharmacologic effects of phenylephrine are similar to those of methoxamine and, specifically, increases in peripheral vascular resistance. Redding and Pearson$^{109}$ observed universal success with defibrillation after intracardiac administration of 10 mg of phenylephrine during ventricular fibrillation. However, no statistically significant differences between epinephrine- and phenylephrine-treated animals were observed with respect to myocardial blood flow, myocardial oxygen delivery and consumption, ini-
tial success of resuscitation, duration of survival, and postresuscitation neurologic recovery.114,115

Ditchey et al.116 reinvestigated the benefits and detriments of β-adrenergic blockade. These investigators initially compared the effects of epinephrine and phenylephrine with those of the β-adrenergic blocking agent propranolol on postresuscitation myocardial ATP and lactate concentrations. They demonstrated a higher myocardial ATP concentration and lower myocardial lactate concentration among animals resuscitated after treatment with both phenylephrine and propranolol compared with epinephrine alone. Phenylephrine with propranolol therefore improved the balance between myocardial oxygen supply and demand during CPR. Our group found better systolic and diastolic myocardial function after successful resuscitation from cardiac arrest among experimental animals treated with phenylephrine; we also documented greater long-term survival rates. With longer durations of untreated cardiac arrest, disproportionately greater myocardial contractile function and postresuscitation survival rates were observed with phenylephrine.105

Only one randomized, double-blind study compared the effects of epinephrine and phenylephrine on the success of clinical resuscitation. Among 65 persons who sustained cardiac arrest outside a hospital, no differences in success of initial resuscitation were observed between epinephrine- and phenylephrine-treated victims.117

Nonadrenergic Vasopressors

Vasopressin. The effects of vasopressin are mediated by activation of two principal receptors, V₁ (V₁a, V₁b) and V₂. V₁a-receptors are located in vascular smooth muscle, myometrium, kidney, spleen, and central nervous system. V₁b-receptors are selectively located in the adenohypophysis, and V₂-receptors are located in cells of the renal collecting ducts. Both V₁a and V₁b-receptors mediate pressor responses and V₂-receptors mediate antidiuretic responses.

The cardiovascular effects of exogenous vasopressin are not well defined, but it is a potent vasoconstrictor agent. Vascular smooth muscle in the skin, skeletal muscle, fat, pancreas, and thyroid gland is most sensitive. Marked vasoconstriction also is induced in the gastrointestinal tract, coronary vessels, and brain. During spontaneous circulation, the initial response is antidiuresis. With higher doses, vasoconstriction is induced, and cardiac output and heart rate are reduced. Coronary vasoconstriction accounts for decreases in coronary blood flow.

Lindner and his associates measured serum concentration of vasopressin. They demonstrated that higher levels of endogenous vaso-
pressin were associated with greater survival rate, and higher endogenous levels of epinephrine and norepinephrine with poor outcomes.\textsuperscript{118} They then compared the effects of low (0.2 U/kg), medium (0.4 U/kg), and high (0.8 U/kg) doses of vasopressin on coronary perfusion pressure and myocardial blood flow during CPR with high-dose epinephrine (0.2 mg/kg) in a porcine model of cardiac arrest and resuscitation. \textit{Medium and high doses of vasopressin produced greater myocardial blood flows and coronary perfusion pressures than medium doses of epinephrine.\textsuperscript{119} Vasopressin was administered to eight in-hospital patients during CPR after use of intravenous epinephrine and external defibrillation failed. After intravenous injection of 40 U of vasopressin, spontaneous circulation was restored in each of the patients, and three patients were discharged from the hospital with normal neurologic function.\textsuperscript{120}}

These favorable results notwithstanding, a more recent study by the same group of investigators demonstrated that vasopressin produced more severe postresuscitation myocardial dysfunction than did epinephrine.\textsuperscript{121} In another series of experiments, the impaired myocardial function was related to a marked increase in systemic vascular resistance after restoration of spontaneous circulation in the vasopressin group. These were associated with statistically significant decreases in postresuscitation cardiac output and myocardial contractility. Accordingly, there is only restrained optimism regarding benefits of vasopressin on long-term survival.

\textit{Angiotensin II.} Angiotensin II is approximately 40 times more potent than norepinephrine. Angiotensin II increases peripheral vascular resistance through its direct and indirect vasoconstrictor effects on precapillary arterioles and postcapillary venules. Vasoconstriction is induced by activation of \textit{AT}_{1}-receptors on vascular smooth muscle cells. Angiotensin II also prompts release of endogenous catecholamines from the adrenal medulla by depolarizing chromaffin cells. When angiotensin II was injected intravenously during CPR, the already greatly increased serum blood concentrations of endogenous epinephrine were further increased more than six times and those of endogenous norepinephrine more than three times.\textsuperscript{122} The effectiveness of angiotensin II as a vasopressor for CPR is largely unexplored. Administration of angiotensin II to pigs doubled myocardial blood flow produced by means of open-chest cardiac massage\textsuperscript{123} and during closed chest compression\textsuperscript{124} compared with saline placebo. At the time of this writing, there is need for objective experimental and clinical data on angiotensin II in settings of CPR before serious consideration can be given to its clinical use.
Buffer Agents

Sodium bicarbonate has been administered during CPR with the assumption that reversal of metabolic and lactic acidosis would favor cardiac resuscitation. In 1961, Jude et al.\textsuperscript{125} proposed that blood pH would best be maintained within normal range during CPR by means of administration of sodium bicarbonate. This was intended to improve cardiac action and augment responsiveness to vasopressor agents. This practice was reinforced in anecdotal reports that suggested that reversal of severe metabolic acidosis during CPR by means of administration of sodium bicarbonate was time-coincident with return of spontaneous circulation. However, experimental and clinical studies did not demonstrate a marked decline in arterial blood pH during the initial 10 minutes of CPR. Though blood bicarbonate content was reduced, hyperventilation accounted for a simultaneous decline in arterial blood PCO\textsubscript{2} such that pH was typically maintained within a normal range or even increased.\textsuperscript{27}

Our group demonstrated with pigs that neither CO\textsubscript{2}-generating buffers nor CO\textsubscript{2}-consuming buffers reversed myocardial hypercarbic acidosis during an 8-minute interval of CPR that followed 4 minutes of untreated cardiac arrest.\textsuperscript{126,127} Each of these hypertonic solutions induced systemic vasodilation independent of their buffer effect and thereby decreased coronary perfusion pressure, which explained, at least in part, the lesser success of resuscitation attempts. Other unfavorable effects of hypertonic buffer agents were demonstrated, including hyperosmolar states, leftward shifts in oxyhemoglobin dissociation, and coronary and systemic venous hypercarbia. A 1995 study did not confirm that buffer agents in settings of CPR increase the vasopressor effects of epinephrine.\textsuperscript{128} Most important, no objective evidence of benefit from the use of hypertonic buffer agents was observed in clinical studies. These were the considerations that prompted the more recent CPR guidelines of the American Heart Association not to advise routine use of buffer agents, especially sodium bicarbonate, for advanced cardiac life support.\textsuperscript{3}

Nevertheless, a study by Vukmir et al.\textsuperscript{129} suggested that a combination of drugs, including sodium bicarbonate, improved outcome for dogs after 15 minutes of untreated cardiac arrest. This finding reawakened the controversy and further stimulated the search for additional understanding of the effects of buffer agents on postresuscitation course. There is evidence that buffer agents may be of benefit after resuscitation from cardiac arrest by means of ameliorating postresuscitation myocardial dysfunction. The organic buffer, tromethamine, was especially effective, possibly because of its capability to reduce myocardial hypercarbia and because of its antiinotropic effect.\textsuperscript{130}
TABLE 4. The effect of buffer agents on outcomes of cardiopulmonary resuscitation

<table>
<thead>
<tr>
<th>Group</th>
<th>No. resuscitated</th>
<th>Survival time (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaHCO₃</td>
<td>4/5</td>
<td>9 ± 2*</td>
</tr>
<tr>
<td>Carbicarb</td>
<td>5/5</td>
<td>34 ± 13*†</td>
</tr>
<tr>
<td>Tromethamine</td>
<td>5/5</td>
<td>35 ± 18†</td>
</tr>
<tr>
<td>Saline placebo</td>
<td>4/5</td>
<td>4 ± 2</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

* p < 0.01 versus saline solution.
† p < 0.01.
‡ p < 0.05 versus NaHCO₃.

The effects of CO₂-consuming buffers and sodium bicarbonate administered during CPR on postresuscitation myocardial dysfunction were investigated by our group.¹³¹ Tromethamine (Tris) served as the organic CO₂-consuming buffer, and Carbicarb (an equimolar concentration of Na₂CO₃ and NaHCO₃) served as the inorganic CO₂-consuming buffer. Postresuscitation left ventricular function was statistically significantly decreased in all animals. Both of the CO₂-consuming buffers, Carbicarb and tromethamine, were associated with a statistically significant reduction in severity of postresuscitation myocardial dysfunction, and this was associated with a significant prolongation of postresuscitation survival (Table 4). When the duration of untreated cardiac arrest was increased and the severity of postresuscitation left ventricular dysfunction was magnified, the benefits of improved postresuscitation myocardial function and survival of the tromethamine- and Carbicarb-treated animals were even more impressive.

We may conclude that buffer agents administered as the only pharmacologic intervention during CPR do not have proved benefits on ability to resuscitate; to the contrary, they have potentially adverse effects. The severity of postresuscitation myocardial dysfunction may be decreased, and the duration of postresuscitation survival may be increased. With respect to postresuscitation myocardial dysfunction, the CO₂-consuming buffers tromethamine and Carbicarb were more effective than CO₂-generating sodium bicarbonate.

Defibrillation

Ventricular fibrillation is the most common cause of sudden death. Rapid correction of VF by delivery of an electric shock to the heart is the definitive treatment and the single most important intervention for successful resuscitation. Both experimental and clinical studies have demonstrated that the likelihood of success of resuscitation and survival is closely re-
lated to the duration of cardiac arrest and more specifically the time that transpires before the first electrical defibrillation attempt.\textsuperscript{26,132}

**Mechanism of Defibrillation**

Although defibrillation has been the most effective therapy for the termination of VF for more than 50 years, the mechanism by which defibrillation restores a perfusing rhythm remains quite controversial. Three hypotheses have been proposed. The *total extinction* hypothesis holds that all fibrillating activity must be extinguished from the ventricular myocardium for successful defibrillation. The *critical mass* hypothesis suggests that defibrillation is achieved when a critical mass, perhaps 75\% of the ventricular myocardium, is depolarized with the electric shock.\textsuperscript{133} Failure to depolarize a sufficient mass of fibrillating myocardium is therefore implicated in failed defibrillation. The *upper limit of vulnerability* hypothesis suggests that fibrillation may be propagated rather than extinguished by the low energy of the delivered electric shock. The energy of the delivered shock should therefore exceed the upper limit of vulnerability of the entire myocardium for successful defibrillation.\textsuperscript{134} Though fundamental differences among the three hypotheses are implied, they all emphasize the importance of delivering electrical power in amounts that terminate VF.

**Power and Waveform of Defibrillation**

The initial recommendation for defibrillation energy from the American Heart Association\textsuperscript{21} was a weight-based power of 6 J/kg. Subsequent experimental and clinical studies, however, demonstrated that lesser power was effective. An electric shock of 200 J or less for a 70 kg man was as effective as 300 J or more.\textsuperscript{135} However, the incidence of atrioventricular block with the higher power was approximately three times greater than that with the lower power. Current recommendations of the American Heart Association\textsuperscript{2} reflect this understanding. The power of the first shock is therefore set at 200 J. Subsequent power levels range from 200 to 300 J. Only the third shock should deliver a maximum power of 360 J. There is no proof of a predictable relation between body size and weight and energy requirement for successful defibrillation of adults. However, transthoracic impedance is the main determinant of the actual power delivered.

The electric current flow actually delivered to the heart is determined by the resistance to current flow, the impedance. Transthoracic impedance is greatly influenced by several variables, including electrode size, electrode skin impedance, and distance between electrodes. The recommended position for the placement of defibrillation electrodes is the anterior-apex position, in which the anterior electrode is placed to the right
of the upper part of the sternum below the clavicle and the apex electrode is placed to the left of the nipple with the center of the electrode in the midaxillary line.²

Transthoracic defibrillators approved for use in the United States, with the single exception of one version of an automated external defibrillator (AED), generate shocks that deliver nominally monophasic, damped sinusoidal waveforms. Functional and morphologic damage to myocardium produced by electrical shocks has been demonstrated.¹³⁵-¹³⁷ The mechanical dysfunction of myocytes after an electric shock depends on the waveforms. Monophasic waveforms produce the greatest injury to myocytes in vitro.¹³⁸,¹³⁹ This triggered both experimental and clinical studies in which the efficacy and safety of monophasic waveforms were compared with biphasic waveforms for transthoracic defibrillation. However, there is a history of effective use of biphasic defibrillation waveforms with automatic implantable defibrillators. The main advantage gained is smaller physical size and markedly lower energy.

Biphasic transthoracic defibrillation with energies of 115 J or 130 J was as effective as monophasic defibrillation with 200 J for 30 survivors of cardiac arrest during implantation of automatic implantable defibrillators.¹⁴⁰ In a multicenter, prospective, randomized study involving 171 patients undergoing electrophysiologic studies, Greene et al.¹⁴¹ compared the efficacy of biphasic waveform defibrillation with that of monophasic waveforms for conversion of ventricular fibrillation or ventricular tachycardia. The first shock converted 75 of 88 patients (85%) with monophasic waveform defibrillation and 81 of 83 patients (98%) with biphasic waveform defibrillation (p < 0.01). Moreover, the first shock in which monophasic waveforms were used converted only 22 of 28 (78%) of the patients with VF, but 25 of 25 (100%) of subjects were converted with biphasic waveform. The power delivered with the biphasic defibrillator was 171 J and with the conventional monophasic defibrillator it was 215 J. As yet, no objective data are available in which these two types of waveform defibrillations are compared in settings of either in-hospital or out-of-hospital cardiac arrest.

Automated External Defibrillators

The first AED was described in 1979.¹⁴² This defibrillator incorporated a digital computer-based rhythm analysis system. Artificial intelligence was provided for decisions about when to deliver a countershock based on the rhythm analysis (Fig. 13). The defibrillation electrodes served dual functions of transducing the ECG signals and delivery of the transthoracic electric shock. When VF or ventricular tachycardia was recognized and con-
firmed with the software, the device was sequenced to charge its capacitor and deliver one countershock at a power later recommended in the American Heart Association Guidelines. The rhythm was re-evaluated, and the capacitor was recharged for the next countershock.

Initial experience has been encouraging. The AED may be the most important advance for improving outcomes of out-of-hospital cardiopulmonary resuscitation. It is in the setting of out-of-hospital cardiac arrest, and specifically sudden death, that the need is most urgent. Unless defibrillation is accomplished within the critical time interval (3 to 5 minutes in the absence of bystander CPR or within 8 minutes if CPR is initiated promptly with present BLS methods), the likelihood of successful resuscitation is remote. First responders may now include defibrillation with AEDs as part of their BLS and thereby improve outcomes. Public access to AEDs has been strongly recommended by an expert panel of the American Heart Association. The general public must be trained in the use of the AEDs if we are to reduce the number of sudden deaths. Public emergency services typically cannot respond within the critical time window of 5 minutes.

There are constraints in the design and operation of current models of AEDs. The time consumed for ECG analysis before delivery of an electric shock ranges from 18 to 28 seconds with five of the currently marketed
models of automatic and semiautomatic defibrillators (Table 5). Chest compression and ventilation are likely to be suspended during this interval lest physical contact with the victim preclude satisfactory rhythm analysis. If the victim is refractory to the initial shock, the sequence of analyses and potential countershocks are repeated three times. This process consumes up to 82 seconds during which CPR is withheld. Such time delays in precordial compression have been experimentally investigated. Unfortunately, these delays greatly compromise success of the resuscitation attempt.26

A second constraint relates to the verbal and visual prompts that guide the user of an AED through the procedure. These prompts are focused almost entirely on the electrical defibrillation process and do not integrate use of AEDs with conventional BLS.

**Postresuscitation Myocardial Dysfunction**

Until recently, CPR research focused primarily on the success of the initial stage of cardiac resuscitation and therapeutic options by which a viable rhythm and spontaneous circulation are restored. We designated this Stage 1 of CPR. However, experimental studies by our group demonstrated substantial impairment of left ventricular function after resuscitation from cardiac arrest, which accounts for a high incidence of postresuscitation deaths. We designated this period Stage 2 of CPR and regard it as important as Stage 1 for long-term survival after successful resuscitation. An increase in postresuscitation functional survival from the current 5% to as little as 10% would serve to save more than 50,000 lives each year, a number that conservatively exceeds the annual total of 43,000 U.S. automobile deaths in 1994.144

Initial studies on postresuscitation myocardial dysfunction were performed by our group on isolated, perfused hearts harvested from Sprague-Dawley rats. After successful resuscitation from ventricular fibrillation of 4 minutes' duration, progressive reductions in contractile function (dP/dt\text{max}) were documented with decreases in myocardial compliance and increases in the slope of the diastolic pressure-volume relation.145 Further investigations were performed on domestic pigs, also after 4 minutes of untreated ventricular fibrillation followed by 8 minutes of precordial compression. After pigs were successfully resuscitated with a 200 J conventional shock, myocardial contractility was strikingly reduced. Stroke volume was reduced to approximately 70% of prearrest values, and ejection fraction declined from 41% to 20%.146 Two discrete dysfunctions were identified. Mechanical dysfunction was characterized by decreased systolic and diastolic function with or without a reduction in arterial pressure.
### TABLE 5. Current marketed models of automatic (AED) and semiautomatic (SAED) defibrillators

<table>
<thead>
<tr>
<th>Device</th>
<th>Manufacturer</th>
<th>Model</th>
<th>Weight (lb, kg)</th>
<th>Analysis pushbutton</th>
<th>Analysis delay prompt</th>
<th>CPR prompt</th>
<th>Time from power on to first shock(s)</th>
<th>Time consumed for delivery of 3 sequential shocks</th>
</tr>
</thead>
<tbody>
<tr>
<td>AED</td>
<td>Laerdal</td>
<td>1000</td>
<td>8.0 (3.6)</td>
<td>No</td>
<td>None</td>
<td>None</td>
<td>18.5</td>
<td>55</td>
</tr>
<tr>
<td>SAED</td>
<td>Laerdal</td>
<td>1000/S</td>
<td>8.0 (3.6)</td>
<td>No</td>
<td>None</td>
<td>None</td>
<td>17.9</td>
<td>50</td>
</tr>
<tr>
<td>SAED</td>
<td>Laerdal</td>
<td>3000/ATS</td>
<td>10.0 (4.5)</td>
<td>Yes</td>
<td>Check patient</td>
<td>None</td>
<td>19.2</td>
<td>50</td>
</tr>
<tr>
<td>SAED</td>
<td>Physiocontrol</td>
<td>510</td>
<td>15.5 (7.0)</td>
<td>Yes</td>
<td>Press to analyze</td>
<td>None</td>
<td>28.4</td>
<td>75</td>
</tr>
<tr>
<td>SAED</td>
<td>Survivalink</td>
<td>9004</td>
<td>7.75 (3.5)</td>
<td>No</td>
<td>None</td>
<td>Begin CPR</td>
<td>22</td>
<td>82</td>
</tr>
<tr>
<td>SAED</td>
<td>Heartstream</td>
<td>S</td>
<td>4.4 (2)</td>
<td>No</td>
<td>None</td>
<td>Begin CPR</td>
<td>17</td>
<td>50</td>
</tr>
</tbody>
</table>
Electrical dysfunction was characterized by potentially fatal ectopic ventricular rhythms. The severity of both mechanical and electrical dysfunctions increased with increasing duration of untreated cardiac arrest. The severity of both increased in pigs that received β-adrenergic agonists, especially epinephrine, during CPR. The severity also increased with increasing CO₂ tension in the myocardium. Finally, severity increased with increasing power of the electrical defibrillator shock. Undefined are (1) the relative importance of global ischemic injury due to interruption of coronary (myocardial) blood flow, (2) the effects of reperfusion, and (3) the thermal effects of electrical injury.

Clinical Significance

Though for approximately 39% of patients (range, 13% to 59%) spontaneous circulation is reestablished, most victims die within 72 hours, primarily of heart failure or recurrent ventricular fibrillation. CPR itself therefore yields a functional survival rate of only 1.4% to 5%. Because myocardial function is substantially impaired after successful resuscitation from cardiac arrest, contractile and hemodynamic function remains impaired for hours or days. The global ischemic injury spontaneously reverses. Our group suggests the term postresuscitation myocardial dysfunction because we initially observed this phenomenon only during analysis of the postresuscitation course of pigs and rats.

Postresuscitation myocardial dysfunction and its fatal outcome have been documented, in part, among patients. In the Brain Resuscitation Clinical Trial I, which included 12 hospitals in nine countries, 262 patients were successfully resuscitated, but approximately 70% died within the first 72 hours. During the first 8 hours after resuscitation, 117 (45%) patients had arterial hypotension, 68 (26%) patients had supraventricular and ventricular arrhythmias, and 66 (25%) had recurrent cardiac arrest as a primary event. In the Brain Resuscitation Clinical Trial II, which involved 24 hospitals in eight countries, 516 patients were resuscitated, and 62% of the patients died within the first week. Most had systemic hypotension.

In studies of the use of high-dose epinephrine in six emergency centers that enrolled 1280 victims of out-of-hospital cardiac arrest, 407 (32%) patients were resuscitated. Though 126 (10%) died before admission to the hospital, almost half of the remaining victims died during the first 72 hours. Arterial hypotension and fatal ventricular arrhythmias were again identified as predominant causes. Only 57 patients (4.5%) were discharged alive from the hospital. In a second multicenter study of the use of high-dose epinephrine, 650 victims of cardiac arrest were enrolled. Spontaneous circulation was initially restored in 132 (20%) patients, but most died
FIG. 14. Reversible myocardial dysfunction after successful resuscitation of pigs. Bl, baseline; VF, ventricular fibrillation; MAP, mean aortic pressure; CI, cardiac index; SVI, stroke volume index; LVSWI, left ventricular stroke work index. (Data from Gazmuri R, et al, unpublished PhD thesis.)

within the first 48 hours, and only 26 (4%) were discharged alive from the hospital.103

Gray et al.152 reviewed 185 incidents of out-of-hospital cardiac arrest in their emergency department over a 19-month period. Only 16 (9%) patients were successfully resuscitated, but none survived hospitalization. Among the 16 initial survivors, the deaths of seven were attributed to refractory hypotension, five to fatal arrhythmias, and four to neurologic causes.

Postresuscitation myocardial dysfunction is reversible, typically over a period of 48 hours in experimental animal models (Fig. 14). Clinical observations of patients are consistent with the experimental findings for animals. For three patients who were resuscitated from ventricular fibrillation after approximately 3, 10, and 30 minutes of cardiac arrest, transthoracic echocardiograms demonstrated decreased ejection fractions.153 Myocardial function was near normal after 2 weeks, and the patients typically had long-term survival. Lewis et al.154 reported that of 248 patients who were discharged alive from the hospital, 77% survived more than one year with negligible deficits. There is substantial evidence that prevention of recurrent cardiac arrest associated with postresuscitation myocardial dysfunction would have substantial likelihood of improving meaningful survival.
Mechanisms

The mechanism responsible for myocardial dysfunction after global myocardial ischemia of cardiac arrest remains unclear. Several hypotheses have been proposed. Postischemic myocardial dysfunction was initially attributed to depletion of high-energy phosphate stores, but the evidence has not fully sustained this concept. Level of intracellular ATP is not consistently predictive of contractile function and cellular viability. When nucleotide precursors of ATPase were administered by means of intracoronary infusion, myocardial function was not enhanced. Moreover, myocardial contractility was increased after inotropic interventions with epinephrine or dobutamine even when ATP level was reduced. Postresuscitation myocardial dysfunction is more likely to be due to impaired energy utilization than to a reduction in energy supply.

The second and newer hypothesis, derived from studies of regional ischemia, is that myocardial dysfunction represents a disturbance in Ca\(^{2+}\) homeostasis in cardiomyocytes. Under normal conditions, intracellular Ca\(^{2+}\) is maintained at very low levels (<100 nM) by the ATP-dependent Ca\(^{2+}\) pump, which moves Ca\(^{2+}\) ions back to storage sites in the sarcoplasmic reticulum. In addition, there is electrogenic Na\(^+\)-Ca\(^{2+}\) exchange on the cell membrane. The action potential that prompts Ca\(^{2+}\) release from Ca\(^{2+}\) stores in the sarcoplasmic reticulum activates actin and myosin, resulting in contraction of myofibers. During ischemia, tissue pH is decreased by means of lactate production, degradation of high-energy phosphate, and reduced removal of CO\(_2\). In addition, free radicals are released by ischemic tissue in a way that injures cell membranes and reduces Na\(^+\)-Ca\(^{2+}\) exchange. Sarcoplasmic reticulum at the same time fails to sequester Ca\(^{2+}\), and cytosolic calcium concentration is increased. The consequent calcium overload reduces the capability for actin-myosin bridging. Accordingly, Ca\(^{2+}\)-triggered myocardial contractility in ischemic or stunned myocardium is reduced.

Diagnosis

The natural history of postresuscitation myocardial dysfunction in patients is not fully understood. The following hemodynamic abnormalities, however, may indicate the presence of postresuscitation myocardial dysfunction: (1) increases in heart rate, (2) decreases in arterial pressure and cardiac output, (3) multiple ventricular arrhythmias, (4) impaired myocardial work capability, and (5) acute ventricular dilatation. Routine hemodynamic and ECG monitoring, including the use of arterial catheters, pulmonary artery flow-directed catheters, and echocardiographic studies during the first 72 hours after successful resuscitation serve as
practical guides for clinical management. However, no specific interventions have been defined.

Continuous measurement of arterial pressure is recommended during the first 72 hours after resuscitation. Arterial pressure reflects overall circulatory status but does not have diagnostic specificity. The balloon-tipped, flow-directed pulmonary artery (Swan-Ganz) catheter allows for differentiation of cardiac failure from hypovolemia by means of evaluation of filling pressures. Higher filling pressures are consistent with cardiac dysfunction. The catheter may be advanced through the subclavian, jugular, brachial, or femoral vein. Mean pulmonary artery pressure and pulmonary artery occlusive pressure may serve as indicators of left ventricular filling pressure, and a thermistor at the tip facilitates cardiac output measurements.

Chest radiographic examination documents the position of endotracheal tubes and intravascular catheters, facilitates differential diagnosis of cardiogenic and noncardiogenic pulmonary edema, and indicates changes in heart size. Increased ventricular filling pressures may be followed by both clinical and radiographic features of pulmonary vascular congestion and edema. Serial chest radiographs are likely to be of benefit in that context. Intermittent Doppler echocardiography has been an important advance for monitoring postresuscitation myocardial function. It provides quantitative assessment of systolic and diastolic functions of both left and right ventricles. Doppler echocardiography provides a uniquely helpful option for early diagnosis, monitoring, and evaluation of therapy.

**Management**

**Pharmacologic Interventions.** The goals of management of postresuscitation myocardial dysfunction are (1) improved myocardial systolic function with increases in stroke volume and reduction of ventricular filling pressures, and (2) control of arrhythmias. The pharmacologic agents available include inotropic agents, specifically dobutamine and phosphodiesterase inhibitors; vasopressor agents, specifically dopamine and levaterenol; and preload and afterload reducing agents, including nitroglycerin, nitroprusside, phosphodiesterase inhibitors, and angiotensin-converting enzyme inhibitors. Though each of these options is cited as appropriate as part of the American Heart Association Guidelines, proof of ultimate benefit is not yet available.

Dobutamine acts primarily on β1- and β2-adrenergic receptors. Its hemodynamic effects include increases in cardiac output and stroke volume, decreases in systemic and pulmonary vascular resistance, and improvement in systemic and coronary blood flow. Though dobutamine improves
postischemic myocardial dysfunction, it has the potential of increasing myocardial oxygen consumption because of its β-adrenergic actions. It may therefore increase myocardial ischemic injury in settings in which coronary blood flow is already reduced.105

Dopexamine is a synthetic analogue related to dopamine with intrinsic activity at both dopamine and β₂-adrenergic receptors. It has shown favorable hemodynamic effects in patients with severe congestive heart failure. The potential role of dopexamine in the setting of postresuscitation myocardial dysfunction remains to be determined.

Phosphodiesterase inhibitors such as amrinone have a combination of inotropic and vasodilator effects. These agents increase the concentration of cAMP and myocardial contractility. Its therapeutic benefit in the setting of postresuscitation myocardial dysfunction is not well established, and the routine use of amrinone carries adverse effects including nausea and vomiting. This drug is best used only after other agents have failed.

Dopamine acts on α-, β-, and dopaminergic-adrenergic receptors. It also prompts norepinephrine release from cellular sites. This adrenergic amine increases myocardial contractility, but in larger doses (<10 μg/kg per minute), α₁-adrenergic actions predominate. The increases in peripheral resistance produced by α-agonists account for increases in afterload such that the workload on the heart and myocardial oxygen requirements are correspondingly increased. The use of dopamine in the postresuscitation setting is therefore restricted to management of life-threatening hypotension. The same considerations apply to the more potent arterial vasoconstrictor, norepinephrine.

Pharmacologic interventions that optimize left ventricular preload and afterload continue to be mainstays for the management of postresuscitation myocardial dysfunction. Nitroglycerin and nitroprusside are the principal venous and arterial vasodilator drugs in current use. At medium and high doses (5 to 10 μg/kg per minute) nitroglycerin relaxes both venous and arterial smooth muscle. The more selective coronary vasodilation produced by nitroglycerin also favors its use in the management of myocardial dysfunction associated with ischemic heart disease. At low doses, nitroglycerin acts primarily as a venodilator, which decreases preload. Intermittent administration of nitroglycerin after 24 hours mitigates tachyphylaxis with loss of hemodynamic efficacy.

Nitroprusside is a rapid-acting venous and arteriolar smooth muscle dilator with a very short half-life. It may increase plasma thiocyanate concentration, induce anion gap acidosis, and rarely produce cyanide toxicity. Its short-term use is not likely to be constrained by these side effects, especially if used in dosages less than 10 μg/kg per minute. Ni-
troprusside is widely used because it is easily titrated in patients who have both arterial and pulmonary artery monitors. For patients with coronary atherosclerosis, coronary vasodilation may reduce blood flow of partially occluded vessels (coronary steal). This may increase anginal episodes in patients with ischemic heart disease despite its favorable systemic effects.

For the management of postresuscitation ventricular dysrhythmia, lidocaine remains the drug of choice even though its ultimate benefit has not been secured. Adenosine has emerged as a first-line drug for management of both atrial and ventricular tachyarrhythmias. It has a short duration of action and therefore induces little adversity. When tachyarrhythmias lead to hemodynamic instability, prompt direct-current cardioversion takes priority. Initial therapy for sinus or atrial bradyarrhythmias with atropine is not usually successful, and temporary insertion of a transvenous pacemaker is specific treatment. Both hypokalemia and hypomagnesemia must be routinely excluded as causes of postischemic arrhythmias.

**Mechanical Interventions.** The rationale for mechanical support of the heart during myocardial dysfunction is to restore hemodynamic stability when pharmacologic interventions fail. However, mechanical support of the heart serves only as a bridge to more invasive interventions rather than as definitive treatment.

**Mechanical ventilation.** The rationale for mechanical ventilation in settings of postresuscitation myocardial dysfunction is to reduce excessive work of breathing. Minimal positive end-expiratory pressure (PEEP) should be applied, and it should be titrated to preclude hemodynamic decrements, especially decreases in cardiac output. Improved systemic oxygenation in settings of pulmonary edema is secured with low-level PEEP (5 cm H2O), and this intervention is likely to reduce intrapulmonary shunting.

**Intra-aortic balloon counterpulsation.** The intra-aortic balloon pump (IABP) is a helium-filled, multichambered balloon catheter advanced into the descending thoracic aorta through the femoral artery. Filling of the balloon is synchronized with the patient's arterial pressure pulse (or triggered by the ECG QRS). The balloon is inflated during diastole and deflated during systole. Accordingly, aortic diastolic pressure and coronary blood flow increase during diastole and when the balloon is inflated. Left ventricular afterload is decreased during systole when the balloon is deflated. IABP support may be lifesaving for patients with postresuscitation myocardial dysfunction whose condition is refractory to pharmacologic interventions, patients with refractory angina, patients with cardiogenic shock, and patients with refractory heart failure. It is a transitional option when other efforts fail.
Conclusion

Despite the universal acceptance and implementation of modern CPR, the science of cardiac resuscitation is in its infancy. CPR is a promise that is largely unfulfilled. Research has evolved slowly with little support. Nevertheless, there is evidence of breakthrough, especially through the introduction of automated external defibrillators and early defibrillation by members of the general public. The ABCs are subject to revision, and D, C, B, A may well represent a more optimal sequence. The history of CPR documents few facts and much lore. The magnitude of the problem deserves the attention of both public and private supporters.

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