Recent Advances in Cardiopulmonary Resuscitation

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Recent Advances in CPR. **Mechanical and pharmacologic measures intended to increase blood flow to vital organs are the mainstay of therapy for patients in cardiac arrest. Several new cardiopulmonary resuscitation (CPR) techniques as well as novel devices and pharmacologic agents have been developed and tested since the first report of manual closed chested CPR over three decades ago. These recent mechanical and pharmacologic advances in the treatment of cardiac arrest are described. Some of these new techniques, devices, and drug therapies are presently undergoing clinical evaluation in patients in cardiac arrest. While many of these new methods and techniques have shown promise in small clinical trials in humans, none have yet to be found to be conclusively superior to manual closed chested CPR and treatment with standard pharmacologic agents.** *(J Cardiovasc Electrophysiol, Vol. 8, pp. 584-600, May 1997)*

curdiac arrest, cardiopulmonary resuscitation, ventricular fibrillation, vasopressin, epinephrine, nitroglycerin, arrhythmia

Introduction

Despite the practice of standard manual cardiopulmonary resuscitation (CPR) for more than 35 years, the vast majority of patients who suffer from an out-of-hospital cardiac arrest die prior to arrival to the hospital.[1-4] Even in regions with highly efficient emergency medical services and well-trained paramedical personnel, survival to hospital discharge from an out-of-hospital cardiac arrest is < 20%. In the United States, the national average for survival at hospital discharge after an out-of-hospital cardiac arrest is < 5%.[1-4]

Multiple factors contribute to the currently poor survival statistics for patients with out-of-hospital cardiac arrest. The time between arrest and initiation of CPR remains the most important factor.[4] Lack of widespread use of bystander CPR as well as delays in arrival between the call for help and arrival to the patient's side by trained health professionals contribute significantly to the high mortality rates. However, in addition to time to initiation of CPR, another critically important factor is the inefficiency associated with the practice of standard CPR itself. Studies in animals as well as in humans reveal that standard CPR provides only 15% to 20% of normal myocardial perfusion and only 25% to 30% of physiologically normal cerebral perfusion.[5,6] Thus, in the best of circumstances, standard CPR can be viewed only as a bridge to more definitive therapy. Although epinephrine administration has also been used for decades to theoretically enhance overall CPR efficacy, recent studies have led to the conclusion that high-dose epinephrine appears to be no better than low-dose epinephrine.[7,8] Moreover, a recent study from Australia suggests that hospital survival is as good with placebo as it is with either high- or low-dose epinephrine.[9] Thus, the inherent inadequacy of standard CPR, even when coupled with presently accepted pharmacotherapy, appears to be a major factor that contributes to the high mortality associated with current CPR techniques.

A third vital factor associated with survival after cardiac arrest relates to the cause of the arrest itself. Malignant tachy- and bradyarrhythmia, se-

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vere left ventricular dysfunction, and acute ischemia lead the list of causes of out-of-hospital cardiac arrest. Although considerable success has been witnessed in the treatment of patients who present with an initial rhythm of ventricular fibrillation, in large part because of the rapid accessibility of early defibrillation, it has been more difficult to effectively treat significant left ventricular dysfunction and acute ischemia in patients with out-of-hospital cardiac arrest.

Recent advances in postresuscitation care, particularly with the development of small implantable cardioverter defibrillators,[10] have helped to rekindle interest in improving the presently dismal outcome for patients with out-of-hospital cardiac arrest. This review article summarizes many of the new advances in mechanical and pharmacologic therapies that are intended to increase the overall efficacy of CPR. The newer mechanical therapies include: vest CPR,[11,12] active compression-decompression (ACD) CPR,[13-17] an intra-aortic perfusion balloon pump,[18,19] an inspiratory impedance threshold valve (ITV),[17,20] interposed abdominal counterpulsation (IAC) CPR,[21-23] and phased thoracic-abdominal compression and decompression.[24,25] The newer pharmacotherapies include: vasopressin,[26-28] angiotensin II,[29] endothelin,[30,31] a combination of epinephrine plus β-adrenergic blockade,[32] vasopressors plus vasodilator (e.g., epinephrine plus nitroglycerin) therapy,[17,33] and the use of antiarrhythmic agents during CPR.[34,35] This article will not discuss new advances in airway management during CPR or new defibrillation techniques.

Background

Mechanical Techniques

To better appreciate the rationale underlying the development of newer mechanical techniques, it is important to understand some of the basic mechanisms underlying standard CPR. The two essential mechanisms thought to promote forward blood flow during standard CPR include: (1) an increase in intrathoracic pressure during the compression phase, which promotes blood flow out of the chest to the brain and other extrathoracic vital organs; and (2) a significant degree of myocardial compression during the compression phase of CPR in some patients, which further promotes forward blood flow out of the chest cavity. Myocardial perfusion occurs predominantly during the decompression phase of CPR secondary to a transient difference between aortic and right atrial pressures.[36-38] All of these mechanisms are dependent, in large part, on the unidirectional cardiac valves. As shown in Figure 1, the "bellows-like" action of standard CPR depends upon active compression and passive relaxation of the chest wall. Intrathoracic pressure tracings during this process reveal that compression during standard CPR increases intrathoracic pressure, and passive relaxation results in a small decrease in intrathoracic pressure relative to atmospheric pressure (Fig. 2). The difference between the diastolic aortic and right atrial pressures, termed the coronary perfusion pressure, is generally considered to be the critical determinant of myocardial perfusion during CPR. All of the newer mechanical means to enhance CPR efficacy have been developed with the goal to either: (a) increase intrathoracic pressure during the compression phase (vest CPR); (b) increase negative intrathoracic pressure during the decompression phase (ACD CPR, the ITV, phased thoracic-abdominal compression and decompression); (c) enhance venous return during the decompression phase (ACD CPR, IAC CPR, the ITV, phased thoracic-abdominal compression and decompression); or (d) enhance myocardial perfusion and brain perfusion during the decompression phase (intra-aortic balloon pump).

Pharmacologic Therapies

The principal drug that has been used to enhance CPR efficacy is the adrenergic agonist epi-

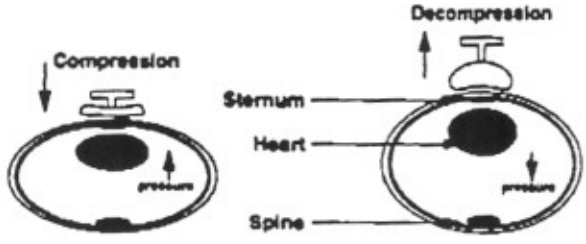

Figure 1. *The chest functions as a bellows during CPR. Both standard and active compression-decompression (ACD) CPR sternal compression lead to an increase in intrathoracic pressure. During the decompression phase, the chest wall recoils during standard CPR due to the natural elasticity of the chest wall musculoskeletal architecture. When the chest is actively lifted upward with the ACD CPR suction device, this results in a lower and prolonged period of negative intrathoracic pressure. The greater the negative intrathoracic pressure during the decompression phase results in greater venous blood return, the greater the myocardial perfusion and increased minute ventilation.*

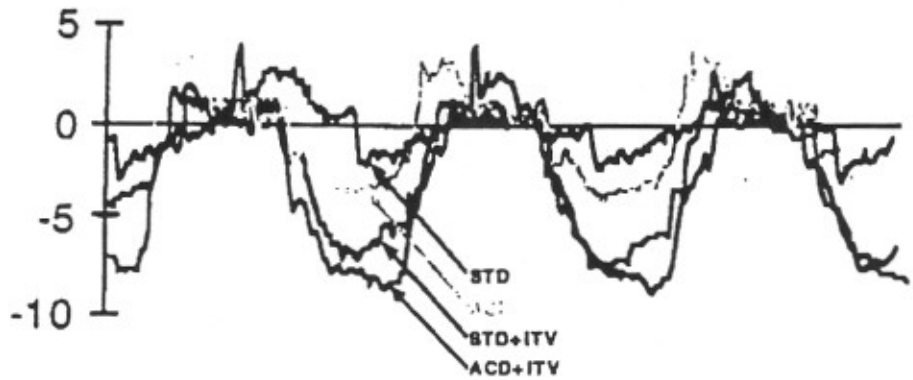

Figure 2. *These representative tracheal pressure tracings were obtained during the performance of standard (STD) and active compression-decompression (ACD) CPR in the presence (+) and absence of an inspiratory impedance threshold valve (ITV) in a pig model of ventricular fibrillation. STD or ACD CPR was performed with an automated pneumatic suction device at a rate of 80 times/min, with the compression depth set to 25% of the anterior-posterior diameter as previously described.[29] Active decompression was performed during ACD CPR such that the chest wall was extended beyond the resting end-expiration position by about 10%. The positive pressures generated with all four techniques were relatively similar. However, the negative intrathoracic pressures during the decompression phase varied depending upon the method of CPR. Addition of the ITV (set to open at −40 cm H_2O) to either STD or ACD CPR results in a marked decrease in intrathoracic pressure. The lower the negative intrathoracic pressure during the decompression phase, the greater the myocardial perfusion.*

nephrine. The α-adrenergic effects of epinephrine increase arterial tone and help to maintain increased aortic pressure. The β_1-adrenergic activity of epinephrine results in both an increase in cardiac inotropy and chronotropy. The β_2-adrenergic effects may cause some peripheral vasodilatation as well as some increase in cardiac inotropy. Although use of epinephrine in animal models as well as in patients in prolonged cardiac arrest results in improved hemodynamic parameters, the use of this potent pharmacologic agent in patients with out-of-hospital cardiac arrest has undergone considerable reassessment in recent years.[7-9,39] Based upon animal studies demonstrating improved efficacy of a "high dose" of epinephrine, there have been a number of randomized clinical trials comparing the potential value of higher versus lower dose epinephrine.[7-9] In general, these studies have demonstrated that there was no benefit of the high-dose epinephrine in patients with cardiac arrest. This may be secondary to the side effects of epinephrine, which include intense coronary artery vasoconstriction, increased myocardial oxygen consumption, and an increased tendency for cerebral edema secondary to profound cerebral artery vasoconstriction.[40,41]

More recently, a study by Woodhouse et al.[9] has brought into the question whether epinephrine is of value at all when compared with placebo in patients in cardiac arrest. The study was originally designed to compared epinephrine (10-mg IV bolus) with placebo. However, given the unease of a placebo arm of the study by a number of medical staff personnel, a large number of patients received the standard 1-mg bolus of epinephrine rather than the blinded therapy with high-dose epinephrine or placebo. As a result, 145 patients received 1 mg of epinephrine, 94 patients received 10 mg of epinephrine, and 100 patients received a placebo. The data were analyzed for each group, and no significant differences were observed in immediate survival (< 10%) or hospital discharge rates (< 2%), regardless of whether the patients received placebo or drug. If there was a small benefit from either low- or high-dose epinephrine, it could not be detected in that study. Thus, although the role of epinephrine is presently controversial, it is clear from this and other studies that if patients require epinephrine, they are de facto in a worse prognostic category and epinephrine administration may not have any impact at all on overall outcome.

Given the multiple potential receptor-mediated effects of epinephrine, a number of other pharmacologic agents have been studied in experimental models, either alone or as combination therapies. These include the use of vasopressin,[26-28] endothelin,[30,31] angiotensin II,[29] methoxamine,[42,43] and phenylephrine.[44] Combination therapies studied more recently include epinephrine plus β-adrenergic blockade,[32-34] vasopressors such as epinephrine or vasopressin together with vasodilators such as ni-

troglycerin,[17-33] and vasopressin plus epinephrine in combination.[33-45] While many of these agents either alone or in combination appear to provide superior vital organ blood flow than "optimal" doses of epinephrine, none have presently undergone sufficient widespread clinical assessment to recommend them as an alternative first-line therapy.

New Mechanical Techniques

As seen in Table 1, there are a number of new and promising mechanical means to enhance vital organ blood flow during the performance of CPR. Some of these techniques involve the use of additional personnel while others involve the use of new mechanical devices. The basic underlying mechanical principles of each one of these advances as well as current data to support their utilization are reviewed below.

Vest CPR

Based on the principle that increases in intrathoracic pressure will result in increased vital organ blood flow, investigators at Johns Hopkins University have been studying the potential value of a circumferential vest as an adjunct to therapy for CPR for over a decade.[11,12] Studies in both animals as well as humans demonstrate that application of circumferential pressure, rather than unidirectional mid-sternal pressure alone, results in a greater increase in intrathoracic pressure and hemodynamic parameters associated with the performance of CPR. As shown in Figure 3, this device (Cardiologic Systems Inc., Hanover, MD, USA) is a bladder-like cuff that can be placed around the arrested patient's chest. Attached to a pneumatically driven motor and pneumatic pump, inflation of the vest at a frequency of 60 to 80 times per minute results in higher arterial systolic pressures in humans as well as greater vital organ blood flow in animal models of CPR. Studies are currently under way to determine whether resuscitation rates can be increased with this technique.

One of the potential benefits of the circumferential vest is the ability to defibrillate the patient using electrodes placed in various locations on the vest itself. Recent data suggest that delivery of high-energy shocks using multiple different vector configurations may be superior to the delivery of a single vector transthoracic shock.[46] As such, the circumferential vest is well suited for multivectorial shock delivery. It is anticipated that within the next 2 to 3 years, smaller pneumatic pumps will be available and that clinical trials will have been completed as part of the assessment of this new technique. The potential role of this device in the prehospital setting remains undefined.

IAC CPR

In an effort to enhance venous return and thereby augment cardiac output, the use of IAC CPR (Fig. 4) has been tested in animal models as well as in humans in cardiac arrest.[21-23,47,48] While it is clear that this technique improves systolic arterial pressures during the performance of CPR, its value in terms of enhancing overall resuscitation rates remains unclear. One large out-of-hospital study demonstrated no benefit of this technique when compared with standard CPR.[23] However, another smaller inhospital study demonstrated a significant improvement in resuscitation rates when compared with standard CPR.[22] In this trial by Sack et al.,[22] 103 patients with inhospital cardiac arrest were randomized to received either standard closed chest CPR or IAC CPR. Nearly twice as many patients had a return of spontaneous circulation in the IAC group ($P < 0.007$), and at hospital discharge, more patients were alive in the IAC group (25%) compared with controls (7%, $P = 0.02$).

As with many of these new potential advances in CPR, clinical trials evaluating IAC CPR are difficult to control. Thus, it is not clear whether the prehospital evaluation of IAC CPR was a fair assessment of the potential value of this CPR technique.[23] It can be quite difficult to control the quality of CPR performance during that kind of study. Similarly, the inhospital study has been criticized for the potential for overenthusiasm of the rescue personnel. In particular, compression force was not controlled and, due to multiple reasons in-

TABLE 1

Interposed abdominal counterpulsation (IAC) CPR
Vest CPR
Active compression-decompression (ACD) CPR
Intra-aortic balloon perfusion pump
Impedance threshold valve (ITV)
Phased thoracic-abdominal compression and decompression

Since the first description of manual closed chest CPR in 1990, several new CPR techniques and devices have been developed. Application of these new approaches in animal models results in improvement in vital organ perfusion and hemodynamic variables associated with an improved prognosis. While each new approach shows promise in humans in cardiac arrest, none of the new techniques and devices has yet to be shown to be conclusively superior to standard manual CPR. All are presently undergoing clinical evaluation in patients in cardiac arrest.

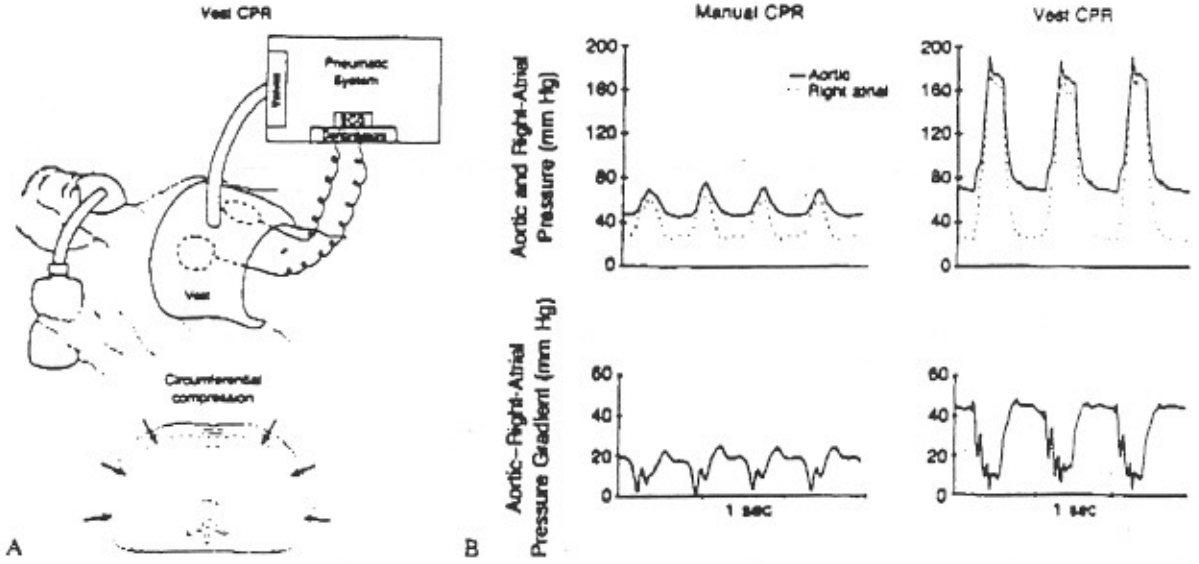

Figure 3. *Vest CPR is based upon the concept that increases in intrathoracic pressure during the compression phase of CPR result in an enhancement of vital organ perfusion. A schematic diagram of the device (A) and representative pressure tracings from patients receiving standard manual CPR and vest CPR (B) are illustrated. The coronary perfusion pressures during both methods of CPR, calculated by the difference between the aortic and right atrial pressures, are also illustrated. (Reprinted by permission of* The New England Journal of Medicine, *from Halperin HR, Tsitlik JE, Gelfand M, et al: A preliminary study of cardiopulmonary resuscitation by circumferential compression of the chest with use of a pneumatic vest. N Engl J Med 1993;329:762-768. Copyright 1993, Massachusetts Medical Society.)*

cluding a lack of adequate rescue personnel at some arrests, a number of patients who should have received IAC CPR only received standard CPR. However, given the relative ease with which IAC CPR can be performed, further clinical evaluation appears to be indicated to determine more definitively the potential role of IAC CPR during resuscitation efforts. IAC CPR requires the assistance of an additional rescuer. Although IAC CPR can be performed with the use of an automated

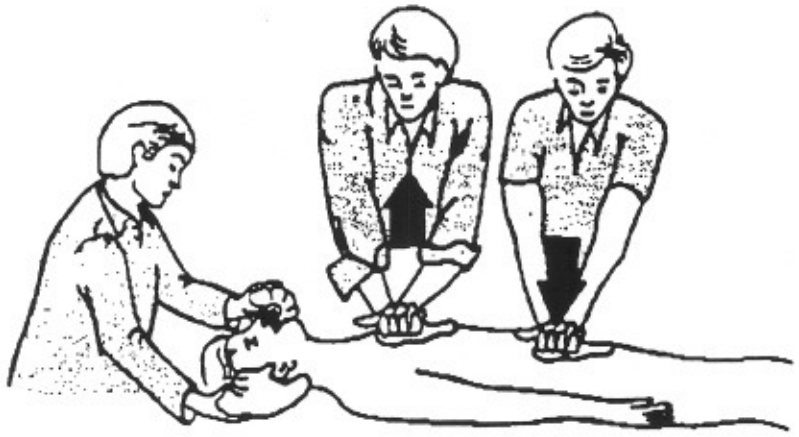

Figure 4. *Performance of interposed abdominal counterpulsation (IAC) CPR is illustrated. During the chest compression phase, no abdominal compression is performed. During the chest wall relaxation phase, abdominal compression results in an increase in venous blood flow to the thorax. In animal models, this counterpulsation technique increases overall cardiac output and myocardial perfusion. (Reproduced with permission from Sack JB, Kesselbrenner MB, Bregman D: Survival from in-hospital cardiac arrest with interposed abdominal counterpulsation during cardiopulmonary resuscitation. JAMA 1992;267:379-385. Copyright 1992, American Medical Association.)*

mechanical chest compression device,[47] such as the Thumper from Michigan Instruments Inc. (Grand Rapids, MI, USA), this approach has some inherent deficiencies. Thumper CPR is not as effective as manual standard CPR,[15] secondary to the fact that chest decompression is impeded by the weight of the compression piston itself. It is possible that a modification of this device, in combination with IAC CPR, may prove to be of benefit in certain clinical settings.

ACD CPR

ACD CPR is a recent modification of standard CPR.[13,17] This technique was developed after a report of a man who used a common household plunger on multiple different occasions to resuscitate his father, who had a history of coronary artery disease.[49] By actively pulling up on the chest with a suction device, ACD CPR serves to increase negative intrathoracic pressure during the decompression phase of CPR. As seen in Figure 1, the active decompression phase results in a greater negative intrathoracic pressure, which enhances both venous return and minute ventilation. Intrathoracic pressures are lower during the decompression phase (Fig. 2) with ACD CPR compared with standard CPR, while positive intrathoracic pressures are similar. As such, ACD CPR is a means to "prime the pump" during resuscitation efforts.

Studies in animal models as well as in humans in prolonged cardiac arrest have demonstrated that vital organ blood flow is significantly increased using ACD CPR when compared with standard CPR.[13-17,50,51] For example, as shown in Figure 7, vital organ blood flow is higher when ACD CPR is performed in a porcine model of ventricular fibrillation when compared with standard CPR. In those studies, the compression depth was set at 25% of the anterior-posterior diameter. Although mathematical models suggest that positive intrathoracic pressures during CPR are more important than increases in negative intrathoracic pressures,[52] experimental evidence has demonstrated that the combination of chest wall compression followed by active decompression provides a significant increase in vital organ pressure when compared with the same degree of chest compression alone.[13,14]

The clinical assessment of patients in cardiac arrest with this technique using a small, hand-held suction device (Ambu, Inc., Glostrup, Denmark; Fig. 5) to provide ACD CPR has, however, been less clear cut. Although hemodynamic improvements have been observed consistently when ACD CPR has been studied in humans, in some clinical settings there has been a significant increase in resuscitation rates with ACD CPR when compared with standard CPR,[16,53] and in other centers no benefit has been observed. The most positive results have been observed in prehospital studies in St. Paul (Minnesota, USA) and Paris (France). In St. Paul, 77 patients received standard CPR and 53 received ACD CPR in a randomized prospective study. This and other studies were terminated prematurely by the United States Food and Drug Administration due to concerns related to study design and lack of informed patient consent. However, at the time the study in St. Paul was stopped, the mean 1-hour survival rate in the ACD CPR group was 40% versus 26% with standard CPR (P

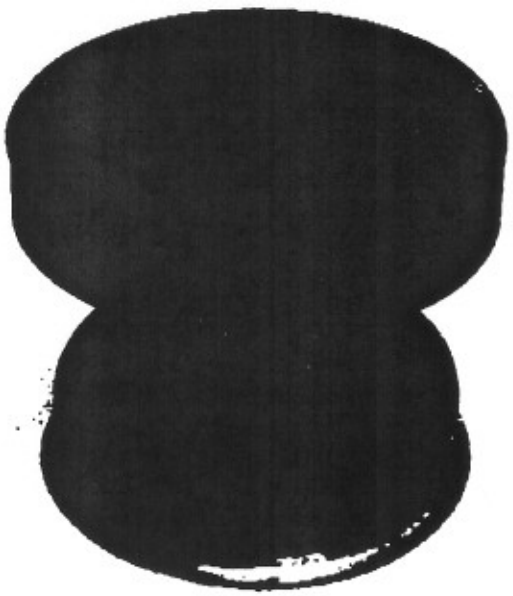

Figure 5. *Active compression decompression (ACD) CPR can be performed with a hand-held suction device.[16] The handle includes a gauge to assist the operator in obtaining the proper depth for active compression and decompression. The silicone suction cup is placed mid-sternum, and ACD CPR is performed at the same rate (80 to 100 times/min) and compression depth (2.5 to 3.0 inches) as standard manual CPR. Decompression is performed by actively pulling up on the handle until just before suction is lost or until a force of −20 to −30 pounds (as shown on the pressure gauge) is achieved. ACD CPR results in improved vital organ blood flow when compared with standard manual CPR.*

< 0.1, 95% confidence interval –2% to 30%). With < 10 minutes between collapse and arrival of the first professional rescue team, 1-hour survival was 59% (19/32) with ACD CPR versus 33% (16/49) with standard CPR ($P < 0.02$). Similar kinds of results were observed in Paris in an out-of-hospital study with 254 patients in the ACD CPR group and 258 patients in the standard CPR group.[53] In Paris, both ACD CPR and standard CPR were used by the first response team, and randomization for the study occurred at the time the mobile intensive care unit arrived to the scene some 17 minutes after receipt of the call for help and approximately 10 minutes after initiation of CPR by the first response team. One-hour survival after cardiac arrest was 37% with ACD CPR versus 25% with standard CPR ($P < 0.003$). Unlike the St. Paul study where hospital discharge rates only trended toward improvement with the ACD CPR technique (23%) when compared with standard CPR (17%), in Paris there was a significant increase in hospital discharge rates with ACD CPR (5.5%) versus 1.9% with standard CPR ($P < 0.03$). A twofold survival benefit was also observed 1 month after hospital discharge.[53]

Counterbalancing these positive results with ACD CPR have been the studies from Ontario (Canada) and California (USA).[54,55] In those studies there was no significant improvement in the primary endpoints with the ACD CPR. In Ontario, 91 (18.2%) patients survived for 1 hour with ACD CPR versus 84.2 (16.5%) with standard CPR ($P = 0.48$), and 23 patients (4.6%) were discharged from the hospital after ACD CPR versus 19 patients (3.7%) with standard CPR.[55] In the combined Fresno and San Francisco California study, 59 patients (14.3%) survived to the intensive care unit with ACD CPR versus 72 patients (16.1%) with standard CPR ($P > 0.5$), and 20 patients (4.5%) were discharged from the hospital after ACD CPR versus 27 patients (6.1%) with standard CPR ($P > 0.6$).[54]

The reasons for the differences between study results are complex and not fully understood. Some of the differences are related to differences in study design, training, differences in response intervals after receiving a call for help, and differences in the overall efficiency and management of emergency medical service systems. In some cities, such as Ottawa (Canada), advanced cardiac life support was not available in the field.[55] In that study, standard CPR was initiated a mean time of 5 minutes after receipt by the rescue team of a call for help, whereas ACD CPR was initiated 9.5 minutes after receipt of a call for help. In addition, in the absence of advanced cardiac life support in the field, both methods of CPR were often performed in a moving ambulance as the patient was rushed to the hospital. Even in the best of circumstances, performance of CPR during transport is challenging.

Other factors that influence the potential benefits of ACD CPR relate to training and the performance of ACD CPR itself, which requires approximately 25% more effort than standard CPR.[56] Proper performance of active decompression of the hand-held device requires significant training and retraining related to the "lifting-up" or decompression phase, and rescuers must know how to use the force gauge. In the California studies, training was performed but without emphasis on how to use the force gauge.[54] One potentially important difference between the studies was that ACD CPR was introduced to the rescue personnel in Canada just prior to initiation of that study. Training was performed at that time. In Paris, ACD CPR had been available and used for more than 2 years prior to initiating the study. As such, the rescue personnel were more familiar with the new technique prior to the Paris study. In addition to training issues, performance of ACD CPR requires more energy and results in more fatigue, at least for some rescuers, compared with standard CPR.[56]

Perhaps the most important difference between the studies in Paris, where ACD CPR was more effective than standard CPR, and other studies involves the concurrent use of an automated ventilator with the performance of both types of CPR. The mechanical ventilators all prevent inflow of respiratory gases except during the delivery of a breath, and consequently the benefit of ACD CPR in Paris may be due to the combination of ACD CPR plus the ITV concept described below. Finally, there are still unknown factors, perhaps similar to those that account for the dramatic differences in outcome after cardiac arrest with standard CPR between different metropolitan areas in the United States.[57,58] For example, in some cities, survival to hospital discharge is 22% and in others < 2%.[14,58] Similar kinds of multifactorial variables may play a role in the disparity of the results with ACD CPR in different cities.

Ultimately, ACD CPR may benefit only a subset of patients in cardiac arrest. Similar to standard CPR, a comprehensive training program is necessary for it to be effectively applied.[56] Though no study has shown a significant drawback from the use of ACD CPR in terms of complication rates or a decrease in survival compared with standard CPR, it is clear from these studies that, despite the

acute hemodynamic benefits that have been consistently observed with this new technique. ACD CPR will not be of benefit in some emergency medical services systems, at least at this point in time.

Clinical trials are still ongoing with this new technique. Based upon the several thousand cases recorded to date, there are no significant negative effects of ACD CPR when compared with standard CPR. However, most of the published studies on ACD CPR have lacked sufficient statistical power to detect small differences, i.e., 10% to 20% improvement in longer-term endpoints such as hospital discharge rates, due to the very low percentage of patients who survive in the control group. For example, in Ottawa, demonstration of a significant improvement from 3.5% survival in the control group to 4.5% survival in the ACD CPR groups would require tens of thousands of patients to achieve an adequate statistical power. Consequently, the potential advantages of ACD CPR when compared with standard CPR remain under further investigation. Due to federal regulatory constraints, it was not possible to complete the initial clinical studies evaluating ACD CPR in the United States.[16,57] These same regulations had prohibited testing of all of the new CPR techniques and pharmacologic solutions described in this report.[57] However, on October 2, 1996, a new federal regulation was signed allowing for resumption of all types of resuscitation research in the United States, even in the absence of informed consent. This will finally enable investigators to proceed with clinical evaluation of all of these new CPR techniques in the clinical setting.

Intra-Aortic Balloon Pump

Based upon the hypothesis that enhancement of coronary perfusion should result in overall improvement of CPR efficacy, some investigators have developed an intra-aortic balloon perfusion pump that serves to provide both pressure support during CPR as well as an access port for the delivery of blood and pharmacologic agents directly into the aortic root.[18,19] Animal studies using this technique have demonstrated significant improvement in overall resuscitation rates and vital organ blood flow when compared with standard CPR.[18] As with the other mechanical advances described above, clinical trials are under way to determine whether or not the theoretical benefits achieved with this technique will be observed in the clinical setting. Although insertion time may be a potential problem with this new technique, standard CPR can be performed while the device is being placed. Moreover, the intra-aortic balloon pump can provide additional hemodynamic support for patients who are resuscitated. It is clear that the myocardium is significantly stunned for many hours after successful resuscitation and may therefore benefit from a balloon pump after successful resuscitation.[59] This technique, like vest CPR, is a more "high-tech" approach to the resuscitation efforts than IAC CPR or ACD CPR. Efforts are under way to try to reduce the size of the intra-aortic balloon pump drive system as well as the catheter itself to facilitate easier and more widespread use of this new technique.

ITV

The ITV (CPRx Inc., Minneapolis, MN, USA) was developed based upon research related to the mechanisms of ACD CPR.[17,20,52] Recognizing that intrathoracic pressures could be lowered further during the decompression phase of ACD CPR with intermittent total occlusion of the airway, this new threshold valve (Fig. 6) can be used with standard CPR, ACD CPR, and vest CPR. By intermittently occluding the airway when ventilation is not performed by the rescuer, negative intrathoracic pressures are enhanced during both standard CPR (Fig. 2) and during the performance of ACD CPR (Fig. 2). When using this valve, ventilation is performed, as with standard CPR, with a 1:5 ratio with chest compressions. During active ventilation, there is no resistance to inhalation or expiration. However, during chest wall decompression in the apneic patient, the impedance valve selectively prevents inspiratory respiratory gas exchange. Its application results in a greater negative intrathoracic pressure, which subsequently enhances venous return and overall cardiac output. In animal models, intermittent inspiratory impedance has been demonstrated to significantly enhance vital organ blood flow when compared with both standard and ACD CPR (Fig. 7).[20,60] In addition, when the ITV was used with ACD CPR, animals were more effectively defibrillated with significantly less energy when compared with ACD CPR alone.[20]

The potential value of enhancing negative intrathoracic pressure during the performance of CPR has been underemphasized until recently. The introduction of ACD CPR has resulted in a renewed appreciation of the importance of negative intrathoracic pressure, both to enhance ventilation and to enhance venous return. Use of

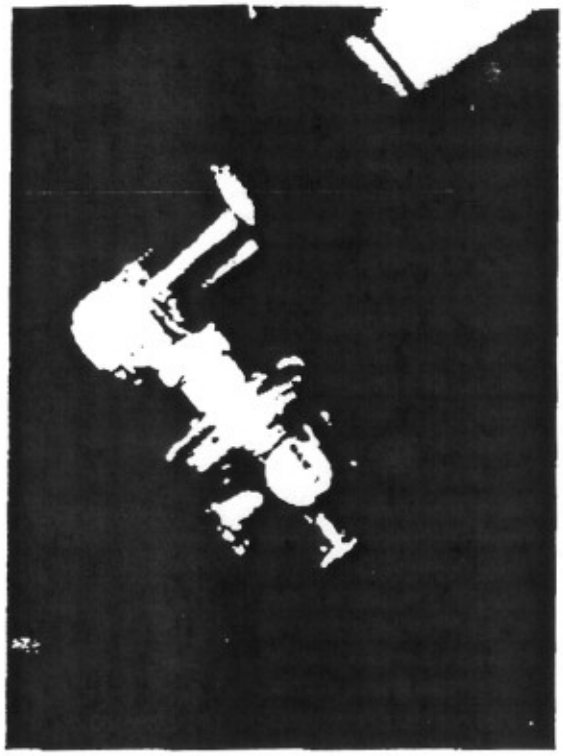

Figure 6. *The inspiratory impedance threshold valve (ITV) is shown inserted between the ventilation bag and the endotracheal tube. In the apneic patient during a cardiac arrest, ventilation is performed every five compressions according to the American Heart Association guidelines as with standard CPR. However, during the decompression phase, the valve closes when the intrathoracic pressure is lower than atmospheric pressure. Closure of the ITV inspiratory threshold valve (set to open at −35 cm H_2O) prevents respiratory gas exchange during the decompression phase and thereby enhances venous blood return to the thorax as intrathoracic pressures equalize with extrathoracic pressures. In animal models, the enhancement in venous return results in increased vital organ perfusion.*

the ITV removes the potential benefits of increased pulmonary ventilation with ACD CPR by preventing respiratory gases from entering the lungs during the decompression phase of CPR, when the patient is not being actively ventilated. However, the prevention of respiratory gas exchange when the patient is not actively ventilated results in enhanced venous return and increased cardiac output, which may be more important than the increasing ventilation in the cardiac arrest setting. As such, the ITV enhances overall myocardial and cerebral perfusion. Preliminary evaluation of the ITV in patients in cardiac arrest has demonstrated an increase in end-tidal CO_2 when compared with standard CPR (Dr. Colin Robertson, personal communication). Further clinical studies are under way to evaluate this potential new technique.

Perhaps the best support for the importance of the inspriatory impedance of respiratory gases to enhance CPR efficacy concept stems from the retrospective recognition of the use of the ITV concept in two studies originally designed to compare standard and ACD CPR. In the first study describing the benefits of ACD CPR in a porcine model of ventricular fibrillation, we utilized a mechanical ventilator that we recognized, only after publication of the manuscript, actually resulted in a comparison of standard CPR plus the ITV versus ACD CPR plus the ITV.[13] By prevention of all inspiration, except when delivered by the automatic ventilator, the complete occlusion of the respiratory circuit by the ventilator resulted in the unrecognized comparison of two methods of CPR, which utilized the impedance threshold concept. This recent observation may help to explain the differences between the results from the ACD CPR study in Paris, Ottawa, and California. In Paris, patients were treated with ACD CPR plus an automatic ventilator. The ventilator prevented all inspiration and, as such, the comparison in Paris was, as in the animal study, an unrecognized comparison between ACD CPR plus inspiratory impedance and standard CPR with inspiratory impedance. In Ottawa and California, the trials compared standard CPR with ACD CPR alone, as bag-valve ventilation was used in most of the cases. It is clear that future studies will need to recognize these fundamental differences in methods of ventilation to truly evaluate the potential benefit of any new CPR technique.

Phased Thoracic-Abdominal Compression and Decompression

The most recent mechanical means to enhance CPR attempts to combine the beneficial features of both ACD CPR and IAC CPR.[24,25,61,62] When simultaneous sternal compression and abdominal decompression are alternated with simultaneous sternal decompression and abdominal compression, venous blood flow to the thorax is enhanced during the chest decompression phase and arterial blood flow to the extrathoracic vital organs is enhanced during the chest compression phase. A manually powered cardiac assist device (Datascope Corp., Fairfield, NJ, USA) has been developed to perform this procedure[24,61,62] (Fig. 8).

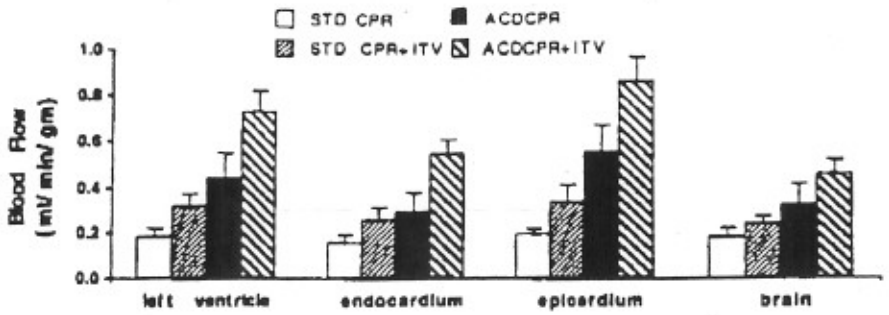

Figure 7. *The graph illustrates the myocardial blood flow achieved during the performance of CPR in a porcine model of ventricular fibrillation. This approach is described briefly in Figure 2 and more fully elsewhere.[20] After 3 minutes of ventricular fibrillation and 2 minutes of CPR, radiolabeled microspheres were injected into the left ventricle. Vital organ blood flow increased with the addition of an impedance threshold valve (ITV) with either standard (STD) or active compression-decompression (ACD) CPR. Myocardial perfusion was as low as 15% to 20% of baseline blood flows with STD CPR and > 50% of baseline blood flow with ACD CPR combined with the ITV. The successive increases in myocardial blood flow correlated with the difference between the diastolic aortic and left ventricular end-diastolic pressures.*

It is constructed with a single rigid frame to which two disposable adhesive-backed pads are attached: one pad attaches to the sternum and the other to the abdomen. The rescuer applies alternating downward forces to the handles located on the sternal and abdominal portions of the device. Studies using this device were recently described in a porcine model of CPR.[24] The results demonstrate a significant improvement in resuscitation rates and 48-hour survival compared with conventional CPR. Similar benefits were observed in the presence of concurrent epinephrine therapy. The initial results in humans demonstrate a significant hemodynamic improvement in hemodynamics in patients in cardiac arrest.[61,62] However, as with the other new techniques described above, clinical trials have been initiated but results are not yet known.

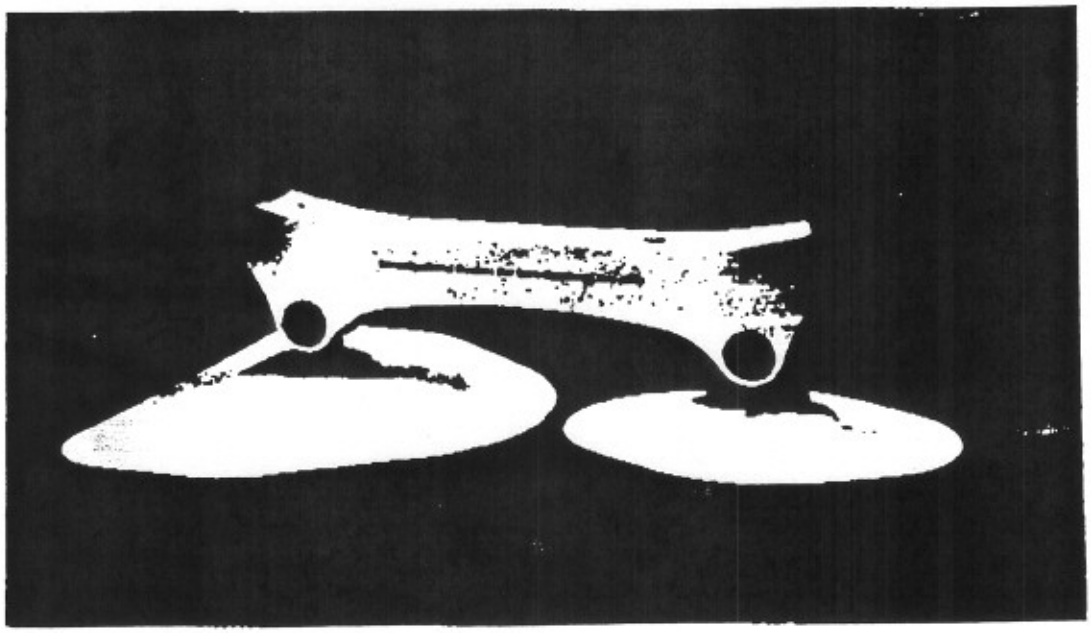

Figure 8. *The "Lifestick™" was recently introduced to perform "phased thoracic-abdominal compression and decompression." This mechanical device attempts to combine the beneficial features of both ACD CPR and IAC CPR.[24,35,61,62] CPR is performed by first compressing the chest and then the abdomen. (Photography courtesy of Roger D. Salls.)*

New Theoretical Advances in Mechanical CPR Techniques

One of the new lessons from ongoing studies on the mechanisms of CPR is the importance of left ventricular end-diastolic pressure in determining overall CPR efficacy. Although the diastolic aortic minus right atrial pressure has been typically used to calculate the coronary perfusion pressure during CPR, the left ventricular end-diastolic pressure appears to be a more important determinant of myocardial, and especially endomyocardial, blood flow.[63] With the introduction of the ITV and simultaneous measurement of aortic, right atrial, and left ventricular pressures, it has become clearer that, at least in animal models, the diastolic aortic minus left ventricular pressure difference appears to be a critical determinant of myocardial blood flow and probably more important than the more traditional aorto–right atrial difference. Recent unpublished data from our laboratories comparing standard and ACD CPR, with and without the use of an impedance valve in a porcine model of CPR, confirm the earlier work of Livesay et al.[63] Using a stepwise logistical regression analysis of multiple variables to further analyze the experiments shown in Figure 7, we observed that the most important hemodynamic variables that influenced the variances in myocardial blood flow were first diastolic aortic pressure, and second left ventricular diastolic pressure. Diastolic right atrial pressures contributed minimally in this analysis. Though somewhat controversial, techniques and pharmacologic agents used to optimize endomyocardial blood flow during CPR may be similar to those that optimize myocardial blood flow in patients with heart failure.[64] As such, we believe more emphasis should be placed in the future upon developing both mechanical and pharmacologic means to enhance the aortic minus left ventricular diastolic differences during CPR.

Pharmacologic Advances in CPR

Given the potential deleterious effects of epinephrine administration during the treatment of cardiac arrest, a number of alternative single or combination therapies have been assessed both in patients and in animal models. These include alternative catecholaminergic agents such as methoxamine, phenylephrine, and norepinephrine, as well as treatment with the vasopressor hormones including arginine vasopressin, angiotensin II, and endothelin. In addition, there is increasing pharmacologic rationale and support for developing a CPR "cocktail," which incorporates the potential benefits of combinations of agents that appear, at least on theoretical grounds, to be superior to single agent therapy. These newer approaches are reviewed below.

Catecholamine Therapies

Based upon the premise that the beneficial effects of epinephrine are secondary to the arterial vasoconstrictor α_1-mediated activity of epinephrine, methoxamine, phenylephrine, and norepinephrine have been assessed in both animals and humans.[41-44,65-70] In animal models, each of these three agents appears to be as good if not better than equipotent doses of epinephrine, and there may be a decrease in postresuscitation tachyarrhythmias. Each of these three catecholamines has also been studied in humans. Despite the potential advantages observed in animal models, clinical trials evaluating resuscitation rates and long-term efficacy have not shown significant benefit. Several recent studies have observed no benefit of methoxamine when compared with epinephrine.[41,68,69] Thus, although deleterious side effects of epinephrine such as the β_1-adrenergic-mediated tachyarrhythmias as well as enhanced myocardial oxygen consumption may be decreased with other catecholamines lacking β_1-adrenoceptor agonist properties, a definitive benefit of the alternative agents has not been demonstrated.

Difficulty with the comparative efficacy trials may be due, in part, to the fact that by the time these agents are delivered, the patients have an extremely low chance of survival. For example, in one large Canadian trial, the survival in the control "low-dose" epinephrine group was < 3%.[7] Timing of drug administration may be the reason why there was no difference observed in the clinical trials comparing high- and low-dose epinephrine. It is noteworthy that in a large trial comparing "low"-dose versus "high"-dose epinephrine, Brown et al.[8] identified a subset of patients, those who received epinephrine within 10 minutes of the call for help, which appeared to benefit from the "high"-dose regimen. However, there were not enough patients in this group to achieve statistical significance. Thus, as with the mechanical devices described above, tens of thousands of patients would be needed to demonstrate any potential statistically significant therapeutic benefit or increased harm with any of these catecholaminergic agents.

Vasopressin

In consideration of potential alternatives to epinephrine, vasopressin appears to hold the most promise.[26-28] The initial interest in the potential value of vasopressin during cardiac arrest stems from the analysis of studies designed to assess the concentrations of different endogenous stress hormones in patients after cardiac arrest.[71] Vasopressin levels were observed to be markedly higher than under normal physiologic conditions.[71] Moreover, the higher the level of vasopressin after a cardiac arrest, the greater the chances of survival.[72] The opposite relationship was observed with epinephrine: higher circulating endogenous epinephrine levels were associated with a poorer prognosis and decreased chance for long-term survival.

Based upon these observations, we have studied the potential value of exogenous vasopressin administration in animals and, more recently, in patients in cardiac arrest.[26-28] In both open chested as well as closed chested models of CPR, administration of vasopressin leads to higher levels of myocardial perfusion for greater periods of time than administration of "optimal" doses of epinephrine. Moreover, cerebral blood flow is significantly greater with vasopressin when compared with epinephrine alone. These results may be due, in part, to prior observations that vasopressin is more effective than epinephrine under conditions of low pH and hypoxia.[73] In addition, although the onset of action of intravenous epinephrine is faster than that of vasopressin, the duration of vasopressin action is significantly longer than that of epinephrine.[45] The effects of "optimal" epinephrine administration are shown in comparison to three different concentrations of vasopressin in Figure 9.[26] In addition to providing superior vital organ blood flow, we observed fewer arrhythmias with vasopressin after cardioversion, and more animals could be successfully resuscitated with vasopressin when compared with optimal doses of epinephrine.[26]

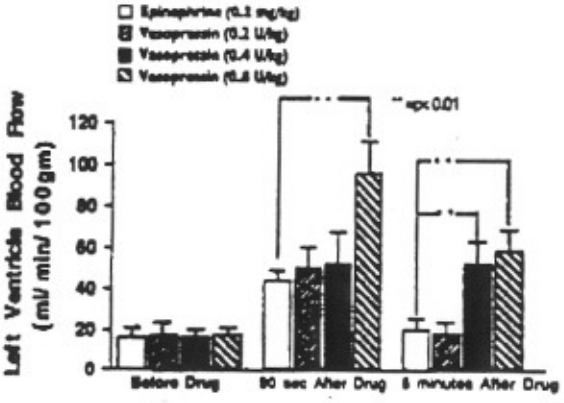

Figure 9. *Exogenous administration of arginine vasopressin during CPR results in more myocardial perfusion when compared with optimal doses of epinephrine. The data demonstrate the beneficial effects of three doses of epinephrine compared with an "optimal" dose of epinephrine in a porcine model of standard CPR. The beneficial effects of vasopressin on enhancement of vital organ blood flow are more pronounced and last longer, in part due to the greater effectiveness of vasopressin under acidotic and hypoxic conditions when compared with epinephrine.*

The mechanism of vasopressin action during cardiac arrest is poorly understood. Hemodynamic measurements suggest that vasopressin causes a profound shunting of blood to the heart and brain and away from the splanchnic region. This may be mediated, in part, by nitric oxide.[74,75] Cerebral blood flow during cardiac arrest and after administration of vasopressin is significantly higher than cerebral blood flow under normal physiologic conditions.[76] Although vasopressin may cause an increase in cardiac oxygen delivery, it may not increase myocardial oxygen consumption as observed with epinephrine therapy. It is likely that the predominant beneficial effects from vasopressin during cardiac arrest are mediated via both V_1 and V_2 receptors.

Based upon the promising animal data, vasopressin has been studied in patients in refractory cardiac arrest and, more recently, in patients with out-of-hospital cardiac arrest in a randomized comparison with epinephrine.[28,77] The first clinical experience in the inhospital cardiac arrest patient population consisted of a series of case reports.[28] Eight patients who developed cardiac arrest refractory to all medical management, including epinephrine administration and direct current (DC) cardioversion, were empirically treated with 40 U of intravenous vasopressin. All eight patients had a return of spontaneous circulation, with the vast majority requiring DC shock for treatment of ventricular fibrillation. Three of the 8 patients were discharged from the hospital in a stable medical condition.

Given the potential promise of vasopressin in patients in cardiac arrest, a small randomized prospective trial was performed comparing epinephrine administration, delivered according to American Heart Association guidelines, with administration of 40 U of vasopressin as first-line drug therapy for patients in ventricular fibrillation.[34] Preliminary results suggests that, compared with epinephrine, vasopressin administration results in a doubling of acute resuscitation, 24-hour survival,

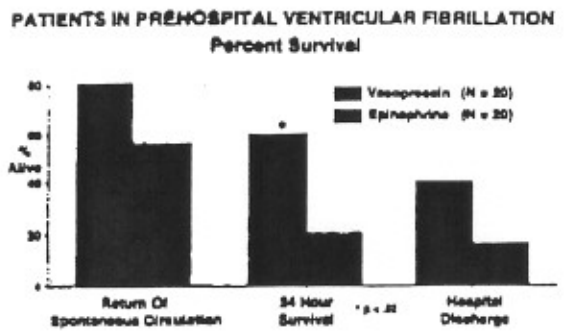

Figure 10. *Administration of vasopressin (40 U) and epinephrine (1 mg) as first-line therapy were compared in a randomized blinded prospective trial in patients with out-of-hospital cardiac arrest and ventricular fibrillation who had failed DC shock therapy. Results of this preliminary study demonstrated a significant improvement in 24-hour survival in the vasopressin group.*[37]

and hospital discharge rates (Fig. 10). Although larger studies will be needed prior to being able to recommend vasopressin as an alternative to epinephrine in patients with cardiac arrest, the encouraging results of these preliminary studies have led the initiation of larger clinical trials of this potent vasoconstrictor.

Angiotensin II

Angiotensin II is another nonadrenergic vasopressor that has been evaluated in animals and in patients in cardiac arrest.[29] Angiotensin II administration results in a significant increase in systolic arterial pressures and vital organ blood flow in animal models of cardiac arrest. This appears to be both a direct effect of angiotensin II on peripheral arteriolar vasoconstriction and also secondary to a massive catecholamine release with adrenergic peripheral vasoconstriction.[29] The clinical experience with angiotensin II is limited at this point in time. It is possible that angiotensin II, when it is in combination with either lower doses of epinephrine, other vasopressor agents, or even low doses of vasodilator therapy, may provide some unique benefit. However, its potential role as a single agent or as part of a CPR "cocktail" is currently quite speculative.

Endothelin

Another nonadrenergic peptide that may have a potential therapeutic role during CPR is the potent vasoconstrictor, endothelin.[30,31,78–80] Similar to vasopressin, we and others have previously observed that endothelin levels are increased in patients in cardiac arrest.[72,78] Endothelin has been studied in animal models of CPR, where it has been observed to increase coronary perfusion pressures and provide higher coronary perfusion pressures during prolonged CPR when compared with epinephrine alone.[30,31] As with many of these new approaches, administration of endothelin has not yet been assessed in patients in cardiac arrest.

Combination Pharmacologic Therapies

In an effort to attenuate the potential detrimental effects of epinephrine on the myocardium, studies have been performed using the combination of epinephrine plus the beta blocker, propranolol.[32] Results of these animal studies demonstrate a significant increase in coronary perfusion pressure and resuscitation rates in animals treated with the combination therapy compared with epinephrine alone. This potentially promising approach has yet to be evaluated clinically.

Another potential approach involves the combination of vasopressors such as epinephrine or vasopressin alone or with vasodilator therapy such as nitroglycerin.[17,33,45,78] We recently assessed the potential benefit of combining moderate doses of vasopressin with epinephrine and compared those results to either agent alone.[45] We observed that, while the vasopressin effect by itself was delayed compared with epinephrine, the epinephrine effect on the coronary perfusion pressure was shorter in duration. In combination, the coronary perfusion pressure was higher for a longer period of time than with either agent alone.[45] The potential clinical relevance of this approach remains under investigation.

The studies combining vasopressor and vasodilator therapies are also promising. The goal of this approach is to increase endomyocardial blood flow by counteracting some of the potent coronary arteriolar vasoconstriction associated with these agents. This approach had been assessed in a pig model of standard CPR using nitroglycerin with either epinephrine or vasopressin.[33] The combination results in a significant enhancement of endocardial blood flow compared with vasopressor therapy alone. In a canine model of ACD CPR, the combination of epinephrine plus nitroglycerin resulted in both an increase in endomyocardial blood flow as well as an increase in total myocardial blood flow compared with epinephrine alone[17] (Fig. 11).

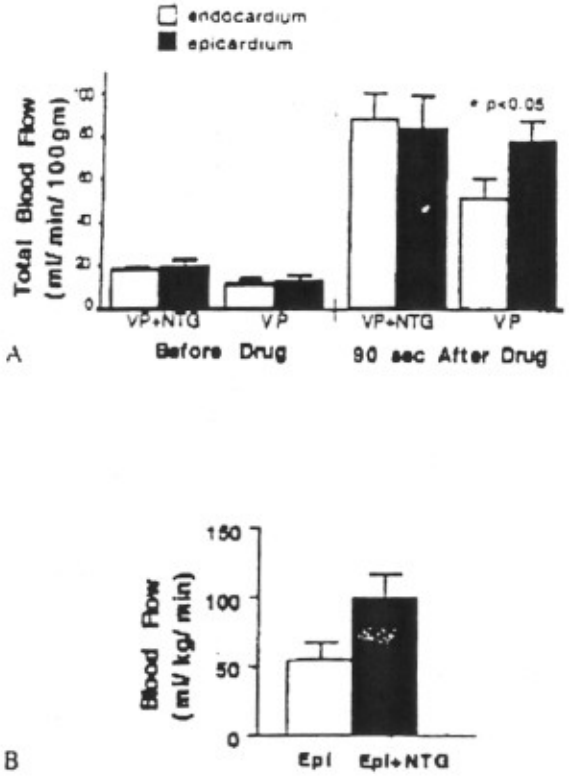

Figure 11. *(A) The synergistic effects of combining arterial vasoconstrictor therapy with nitroglycerin, a venodilator and coronary artery vasodilator, are illustrated during both standard CPR and with ACD CPR. When vasopressin (VP, 0.4 U/kg) was combined with nitroglycerin (NTG, 5 μg/kg), there was a shift in blood flow from the epicardium to the endocardium with no change in total myocardial blood flow during performance of standard CPR in a pig model of cardiac arrest. (B) In a canine model of cardiac arrest and ACD CPR, addition of nitroglycerin (NTG, 10 μg/kg) to concurrent epinephrine therapy (Epi, 1 mg) resulted in an increase in total myocardial perfusion ($p < 0.05$) as well as an increase in endocardial blood flow when compared with epinephrine alone.*

The potential importance of enhancing endocardial blood flow during CPR cannot be underestimated.[83] Both epinephrine and vasopressin alone predominantly increase epicardial blood flow. As with acute ischemia and severe heart failure, interventions that increase endocardial blood flow may be fundamental to an effective pharmacologic resuscitation scheme. Although it may be considered an anathema to administer nitroglycerin to a patient in cardiac arrest, a combination of vasopressor and vasodilator treatment is frequently used in patients in severe heart failure or when vasopressin is used to treat variceal bleeding.[81-83] We believe that a similar kind of pharmacologic mechanistic benefit may be possible when nitroglycerin or other predominantly coronary artery vasodilators and venodilators are used in combination with potent vasoconstrictor agents such as vasopressin and epinephrine. This combination has not yet been assessed in humans in cardiac arrest.

Antiarrhythmic Agents

Antiarrhythmic agents are typically reserved for administration after successful resuscitation. However, administration of antifibrillatory therapy may be important in patients with refractory ventricular fibrillation and ventricular tachycardia.[34,84,85] Although not a standard part of the advanced cardiac life support system algorithm, administration of certain antiarrhythmic agents may be of benefit. Clearly, these agents may play a critical role in stabilizing the electrical activity of the recently resuscitated state. Some of these agents have significant negative inotropic properties and, for that reason, are not typically given during CPR. However, intravenous lidocaine, procainamide, bretyllium, and amiodarone may have value during the performance of CPR.

Intravenous lidocaine, procainamide, and bretyllium have been used for decades in this setting. Although they all demonstrate potential benefit in animal models, it has been difficult to prove the efficacy of each of these agents in the setting of cardiopulmonary resuscitation. Perhaps the most promising is intravenous amiodarone therapy.[35,84,85] Based upon a small study that showed a benefit in patients in refractory cardiac arrest,[35] larger clinical trials are under way outside of the United States.

The Ideal CPR "Cocktail"

It is unlikely that a single pharmacologic agent will be sufficient to maximize all of the necessary cardiovascular activities needed to optimize the chances for successful resuscitation after cardiac arrest. Early animal data suggest that blunting of some of the β-adrenergic activity of epinephrine would be of benefit during administration of epinephrine.[32] Here the potential beneficial effects of the α-adrenergic activity of epinephrine are counterbalanced by the deleterious effects of the β-adrenergic activity. Although considerable animal research will be necessary prior to testing the concept of a CPR cocktail in humans, preliminary data also suggest that a combination of epinephrine plus vasopressin may be superior to epinephrine alone.[32]

Moreover, the addition of a coronary artery vasodilator like nitroglycerin to a vasopressor cocktail may have further distinct advantages.[13] Furthermore, agents that appear to be protective of cerebral function, such as mannitol, as well as corticosteroids may eventually be found to be important in such a cocktail solution. Though difficult to assess because of the multiple potential permutations of different drug concentrations whenever combination therapy is used, this approach is theoretically sound and we believe should be promoted.

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