A THREE PHASE TEMPORAL MODEL FOR CARDIOPULMONARY RESUSCITATION FOLLOWING CARDIAC ARREST

MYRON L. WEISFELDT, M.D.

BALTIMORE, MARYLAND

ABSTRACT

Data from a wide variety of studies suggests that survival from cardiac arrest is very much dependent on the implementation of therapeutic maneuvers in a sequence. Emphasis is on the time from the onset of cardiac arrest to the beginning of resuscitative maneuvers. For example, the optimal timing of defibrillation in a patient with ventricular fibrillation is one major issue, but is in part dependent upon having a defibrillating device available. As well, providing artificial circulation requires the presence of a bystander or a resuscitation team ready and willing to perform cardiopulmonary resuscitation. At some point resuscitation includes dealing with the metabolic consequences of prolonged cardiac arrest. This may require drugs or agents that mitigate the longer term consequences of metabolic factors that arise after cardiac arrest and a prolonged period of ischemia.

BACKGROUND

In an effort to be specific, Lance Becker and I (1) recently proposed a temporal sequence of phases of cardiopulmonary resuscitation. Since the publication of this first article, several new pieces of data have reinforced the concepts. There have been several articles that have proposed practical guidelines based on the model as proposed. The model has been refined further in this discussion.

As listed in Table 1, Phase I of the model is between 0 and 4 minutes following cardiac arrest. During this interval optimal resuscitation occurs with purely correction of an electrical problem by defibrillation in the case of ventricular tachycardia or fibrillation, or pacing in the setting of bradycardia.

Phase II is the circulatory phase of cardiac resuscitation and begins at about four minutes after cardiac arrest and continues for at least ten minutes. This is a phase in which optimal results occur with providing

---

William Osler Professor of medicine Johns Hopkins Medicine 1830 East Monument Street, Suite 9026 Baltimore, MD 21287 mlw5@jhmi.edu

Presented to the American Clinical and Climatological Association October 16, 2003

115
artificial circulation through cardiopulmonary resuscitation. At an appropriate interval *after* providing circulatory support, defibrillation is required for ventricular fibrillation or tachycardia, or again pacing intervention if there is asystole. It should be noted that often in pure bradycardia, circulation alone and/or mechanical effects of chest compression will result in cardiac contraction and return of pacemaker activity.

The Phase III of the model is a metabolic phase which is thought to begin as a substantial contributor to failure of cardiac resuscitation after about ten minutes of cardiac arrest. The existence of the metabolic phase is somewhat speculative, and the mechanisms for mitigating the metabolic phase are even more speculative. But, I will take the liberty of presenting evidence supporting the existence of profoundly important metabolic factors, and the possibility of their mitigation by means of active treatment.

### PHASE I

Turning first to the electrical phase of cardiac arrest, there can be no question that the extensive experience with the automatic implantable defibrillator shows that defibrillation occurring 15 to 20 seconds after the onset of what would be a lethal ventricular tachycardia, or ventricular fibrillation, is almost uniformly lifesaving. Survival rates (2) from the arrhythmia with an implantable defibrillator exceed 95% in most series. At this time point, there is clearly no need for artificial circulation and there is little or no metabolic or cardiac embarrassment.

A number of large population studies have shown a progressive time-related fall in short-term and long-term survival from cardiac arrest dependent on the time to defibrillation. (3). In simple terms, these data in thousands of patients suggest that there is approximately a 10% fall in survival with every minute that passes before defibrillation occurs. Accepting these data one would predict that defibrillation at three minutes after cardiac arrest would result in 70% survival, five minutes after cardiac arrest 50% survival, and 10 minutes after cardiac arrest less than 5% survival. Whether this in fact is a smooth mathematical relationship between survival and time to
defibrillation is not in my mind entirely clear. In most settings where large population studies have been done, major efforts have been made to try to properly time the onset of cardiac arrest to defibrillation, but to some degree these time intervals are an estimate. It is possible that there is a gentler fall-off in resuscitation success over the first few minutes (perhaps the first three or four minutes), and then a steeper fall at time intervals after four minutes when defibrillation is done particularly in the absence of CPR. Experimental animal studies as noted below suggest that this speculation may in fact be correct; for some minutes, defibrillation alone results in very high survival with a very rapid fall-off in the absence of artificial circulation in four to five minutes.

Some support for the model comes from the data available in studies of automatic external defibrillators (AEDs) in the hands of trained individuals with a duty to respond to emergencies. The first major study supporting the value of AEDs was done by Roger White and his colleagues in Rochester, MI (4) by placing defibrillators into police vehicles. Over a six-year period the nearest police cars as well as nearest EMS paramedics were summoned to the scene of an apparent cardiac arrest. Approximately 40% of the time the police reached the victim before the paramedics and provided defibrillation as appropriate, and then if there was no response, went on to provide CPR. In this study overall the police were as successful at resuscitation as the paramedics. The overall survival rate in this study was 40.5% of 131 patients in ventricular fibrillation. A tremendous effort was made to properly time the performance of defibrillation. This very high survival rate was associated with a mean time to defibrillation of 5.5 minutes entirely consistent with the model. In this study, 68% of the patient had returned spontaneous circulation at the scene of the cardiac arrest.

Three studies have been published in the New England Journal of Medicine reporting results of AED programs in three settings: casinos of Las Vegas, airplanes and airports of the City of Chicago. In these studies time to defibrillation on the average was approximately the same as the Rochester study. Survival rates were more than 50% in 90 victims in the casinos of Las Vegas (5) greater than 50% in 18 victims in the Chicago airports (6) and in 25% in 13 victims in American Airlines planes (7).

**PHASE II**

The second phase of cardiac arrest is the circulatory phase beginning at about four minutes after cardiac arrest and extending to at least ten
minutes after cardiac arrest. Initial animal studies by Niemann and others (8,9) showed that in animals defibrillation after four to five minutes of ventricular fibrillation without CPR resulted in asystole which was refractory to further resuscitative measures. If the period of cardiac arrest was extended but CPR was performed during the additional time of cardiac arrest, defibrillation was effective in restoring cardiac rhythm. More recently, extremely impressive studies have been reported by Steen and associates (10). These investigators studied pigs subject to ventricular fibrillatory arrest for 6-1/2 minutes before any resuscitative measures were undertaken. If after 6-1/2 minutes of ventricular fibrillation, defibrillation alone was done, one of the six pigs studied had returned spontaneous circulation. If CPR was performed for 3-1/2 minutes of continued ventricular fibrillation followed by defibrillation, five of six survived. If CPR was performed and then as is true with current AED defibrillators, a 40-second period of ventricular fibrillation occurs without CPR before the shock was actually delivered, then only one of the six pigs subjected to this sequence survived. Thus, it is not only the need of doing CPR and creating circulation during the circulatory phase, but the circulation must be maintained essentially without interruption to the point of defibrillation in order to have maximum survival benefit.

The initial human study of the need for circulation was performed by Leonard Cobb and associates in Seattle Washington (11). Between 1990 and 1993, Cobb had his advanced cardiac life support teams do defibrillation first before cardiopulmonary resuscitation was routinely performed (except by bystanders). In 1994 based upon the animal data, Cobb changed the protocol to performing 90 seconds of CPR before defibrillation, again, regardless of the time of arrival. This study demonstrated that for the longer time from the onset of cardiac arrest to arrival of the unit, there was a survival advantage in the 1994 to 1996 period when the CPR was done before defibrillation. This is consistent with the animal models.

Very recently, a randomized prospective clinical trial of CPR first before defibrillation was performed by Wik and his colleagues in Norway (12). These investigators randomized 200 patients with out-of-hospital ventricular fibrillation to either standard care with immediate defibrillation or CPR first, with three minutes of basic CPR by ambulance personnel prior to defibrillation. If the initial defibrillation was unsuccessful, the standard group received one minute of CPR before additional defibrillation was attempted. The authors of this study pre-specified two subgroups for analysis: Those with an estimated response time of less than and greater than five minutes. In the total
PHASES OF CPR

group, there was 22% survival with CPR first and 15% survival in those in the control or defibrillation first group. In the pre-specified sub-group of less than five minutes of response time, there was a 29% survival in the control arm and 23% survival in the CPR first arm, which was not statistically significant. The trend was in favor of defibrillation first. Strikingly, in the group with greater than five minutes response time, there was a 22% survival rate in the CPR first group, and a 2% survival in the control group. This difference was highly statistically significant (p < .006).

Finally, in a retrospective non-prespecified sub-group analysis of White data from Rochester, survival after five minutes of cardiac arrest was greater with CPR performed first consistent with the above two studies. Over time there have been a number of efforts to improve the effectiveness of artificial circulation performed during cardiopulmonary resuscitation. Those efforts have begun to show signs of success in terms of improving the hemodynamics of resuscitation as well as at least return of spontaneous circulation. Long term survival benefits have not yet been established for any technique or devise alternative to conventional cardiopulmonary resuscitation.

PHASE III

The final and most speculative portion of the 3-phase model is the metabolic phase of resuscitation. By far the most impressive studies supporting a metabolic phase are two recently published studies on hypothermia induced in the emergency department in subjects who failed to regain consciousness. In a European study done by Holzer, et al., and an Australian study done by Bernard, et al. (13,14), both showed that body surface cooling to 32° to 34° centigrade and maintained for 24 to 48 hours improved long-term survival. Each study was statistically significant. There was one life saved for every seven patients cooled, a fairly impressive therapeutic result.

One of the remarkable aspects of clinical state of understanding of cardiac arrest and resuscitation is that no single pharmacologic agent has proven to have survival benefit. Certainly, the most uniformly accepted drug is intravenous epinephrine. In experimental animals a single dose of high dose epinephrine has been shown to be effective. In man, a number of randomized studies of high dose versus ordinary dose epinephrine failed to show any survival advantage. One possibility is that a single dose of epinephrine early in cardiopulmonary resuscitation causes peripheral vasoconstriction, and an improvement in coronary flow, and thus better circulation in the circulatory phase.
Some years ago we showed (15) in the dog that as epinephrine increased brain and myocardial blood flow during cardiopulmonary resuscitation, but strikingly decreased renal and small intestinal blood flow. Perhaps larger or repeated doses lead to gut and/or renal injury. A number of studies in man have suggested that endotoxemia or gram-negative sepsis is a consequence of prolonged cardiac arrest. These observations raised the possibility that epinephrine may induce gut ischemia and greater ability of bacteria to pass the intestinal barrier leading to gram-negative sepsis and endotoxemia and metabolic embarrassment. (16)

Melissa Burne-Taney and Hamid Rabb (17) in our laboratories recently showed that T-cell deficient mice are significantly protected from acute renal failure following cardiac arrest and cardiopulmonary resuscitation. These results would suggest that there is profound activation of the inflammatory system in a broad, generalized and destructive format as a part of this syndrome of cardiac arrest and resuscitation with metabolic embarrassment. Clearly, there is much work to be done and much to be learned.

Finally, I would point to a patient study of Gerald Buckberg and associates published some years ago (18). This is a series of case reports of 14 patients with in-hospital witnessed cardiac arrest ongoing from 22 to 150 minutes with ventricular fibrillation and CPR. These individuals had known heart disease. They were taken to the operating room after the failure of resuscitation. The left ventricle was vented after placement on cardiopulmonary bypass and warm aspartate glutamate blood cardioplegia was used for 20 minute period. The surgeon then corrected cardiac abnormalities as feasible. Remarkably, 11 of these 14 individuals survived three to nine months. The question, of course, is what was the effective agent to reverse these long-term cardiac arrests. Was it in fact only better circulation, or was it better circulation along with removal of toxic products through the cardioplegic heart/lung bypass system?

Thus, we are left with a number of major questions about this metabolic phase of cardiac arrest therapy. What are the key metabolic mechanisms for whole body ischemic injury? And, what are the mechanisms that could be used toward ischemic tolerance in addition to hypothermia? Are there really toxins produced or toxic products that could be specifically antagonized?

CONCLUSION

There is very strong evidence to support the value of immediate defibrillation or electrical intervention during the first few minutes of
cardiac arrest. There is increasing evidence that after four minutes artificial circulation before defibrillation is critical to optimizing survival.

Despite artificial circulation and proper electrical treatment, survival is poor at greater than ten minutes of cardiac arrest when there is increasing evidence of metabolic embarrassment that has its own set of causal factors and its own set of potential remedies. Many of these are yet to be specifically discovered.

REFERENCES

1. Weisfeldt ML, Becker LB. Resuscitation After Cardiac Arrest, JAMA 2002;288: 3035–3038


DISCUSSION

Gersh, Rochester: Mike, the comment about hypothermia in the winter Rockies contributing to the presentation of viable neurologic function, is actually not correct, because if you’ve been there in winter, you’ll find that no one is ever outside. But on a more practical and hopeful note, one of our fellows, Dr. Thomas Bunch has recently completed the follow-up of those witnessed out of hospital cardiac arrest survivors who left hospital. And the follow-up at five years is absolutely extraordinary. Survival is very similar to that of age and sex marker controls. Of those who had been working before their out of hospital cardiac arrest, about 80% of them are still working. And neurologic function in a sub-study of that appears to be intact. It shows what can be done in a small community where Dr. Roger White as you pointed out, really has made an enormous contribution.

Weisfeldt, Baltimore: Thank you for the comment.

Alpert, Tucson: Mike as you know, the group at Arizona for many years before I came, Gordon Ewy, Bob Berg, and Carl Kern have been interested in CPR research. Recently in their animal model, they have shown that the respiring patient may actually be harmful, and you didn’t mention that. Do you subscribe to that? Should we stop trying to do the respiration and really just concentrate on doing effective CPR?

Weisfeldt: I would rather put the other way, saying that it’s absolutely clear that if you don’t want to ventilate, and you just compress the chest, that’s going to produce a clear beneficial effect. There isn’t much the question, as CPR goes on longer the need for ventilation increases, but I think that the caveat you’re talking about is probably correct. In the first few minutes, after cardiac arrest you have plenty of oxygen around, you don’t need to ventilate, and ventilation may be harmful. We have no data on this, but one of the rationale for the flipping the patient over on their stomach was in fact the idea at least in the field, the tongue would fall forward and you might in fact get much better ventilation in that way than in conventional CPR. The study, as I commented was very difficult to get approved, and we certainly had no ability to interrupt tracheal intubation and ventilation. If you want to think about a problem that’s really challenging think about how one is going to do research to extend this issue of compression on the back, because it’s so ingrained in everybody’s mind that compression on the sternum is the way to do good. The notion of informed consent or a waiver would be very challenging. We really have not been able to figure out a way to extend that observation into a clinical trial that would be approvable and viewed as ethical and reasonable.