

# Optimal timing of electrical defibrillation in out-of-hospital ventricular fibrillation

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## ABSTRACT

Although current guidelines on cardiopulmonary resuscitation (CPR) advocate prompt defibrillation of ventricular fibrillation in a cardiac arrest situation, evidence has recently been accumulating indicating that the optimal approach to the treatment of these patient may not be immediate defibrillation. Research in animals as well as recent human studies show that a period of CPR before defibrillation results in better survival, particularly if the time from the onset of ventricular fibrillation exceeds several minutes. This review summarises the basis for this concept and briefly discusses the human studies on early versus late defibrillation.

There is ample, scientifically rigorous evidence that defibrillation is the definitive treatment for ventricular fibrillation (VF) (1). Early defibrillation within the first few minutes of VF has an excellent chance of restoring a perfusing rhythm and thus rescuing the patient from an otherwise certain death. Moreover, the quickly revived patient often suffers little or no loss in quality of life due to, for example, neurological damage.

However, the window of opportunity for a happy outcome through defibrillation is short. The chance for successful defibrillation (defined as termination of VF and restoration of a perfusing rhythm) diminishes significantly already within the first minutes of VF (1). Often defibrillation after prolonged VF results in an even less desirable rhythm such as pulseless electrical activity (PEA) or asystole (ASY) for which there is no effective therapy.

It has been assumed that by maintaining a rudimentary circulation through basic cardiopulmonary resuscitation (CPR), these processes of deterioration of the defibrillation success rate and development of neurological damage can, to some degree, be counteracted. In accordance with this, patients who have received CPR from bystanders have better observed rates of survival than those who have had to wait for first responding units without any treatment (2).

Hence, the recommendations of the current international guidelines for resuscitation (1) are highly rational in implying that the patient should receive basic CPR until a defibrillator is available, at which point electrical defibrillation of VF or ventricular tachycardia (VT) should take priority over other resuscitative efforts. Evidence has been accumulating for some time now suggesting that it may not be optimal to prioritize defibrillation over CPR in all cases of VF. It would seem that when VF has persisted for some minimum time (perhaps

around 4-5 minutes), delaying defibrillation to provide a short period of CPR (current human studies have used 90-180 seconds) could be beneficial. The first evidence came from experimental animal studies (3-7), and recently two human studies (8,9), have given similar results. It is the purpose of this review to present the evidence and discuss possible implications of it and considerations en route to applying the evidence to clinical practice and guidelines.

## The trial by Cobb et al

In an externally controlled trial by Cobb et al (8) conducted in Seattle, Washington between July 1, 1990 and December 31, 1996, the investigators modified the protocol used by first-arriving emergency medical technicians (EMTs) to treat cardiac arrest by inserting 90 seconds of CPR before the application of the automatic external defibrillator (AED). The study included 1117 patients aged more than 18 years with VF as the initial cardiac rhythm. During the pre-intervention period (July 1, 1990 to December 31, 1993), immediate defibrillation had the highest priority, and EMTs were to apply the AED as soon as it was made ready for use. Main outcome variables were survival to hospital discharge and neurological status at hospital discharge. Results were analyzed separately for the entire study population and for the subgroups of patients with response times less than 4 minutes and 4 minutes or more. The article does not mention whether the decision to use 4 minutes as a cutoff point for response intervals was made prior to data analysis.

The results are summarized in Table 1. Survival to hospital discharge improved modestly but still significantly from 24% to 30% ( $p = 0.04$ ). The benefit was predominantly seen in patients for whom the initial response interval (the time from dispatch to arrival of the first-responding unit) had been 4 minutes or more (survival rates of 17% versus 27%;  $p = 0.02$ ). The proportion of all patients who survived with

favorable neurological outcome increased from 17% to 23% ( $p = 0.01$ ). However, the proportion of survivors with favorable neurological outcome did not increase (71% vs. 79%,  $p < 0.11$ ). Somewhat unexpectedly, a significant increase in the incidence of favorable neurological outcomes was seen in favor of the intervention period in patients for whom initial response intervals were less than 4 minutes (87% vs 67%;  $p < 0.002$ ). This, however, was not an a priori hypothesis.

The authors concluded that the survival of patients treated for out-of-hospital VF during the intervention period was significantly improved compared to survival during the pre-intervention period encompassing the preceding 42 months. They further concluded that the improvement was most evident in cases where the first responding unit arrived 4 minutes or later after dispatch. While the authors conceded that other reasons for the improved survival rates besides the protocol modification could not be excluded, they deemed them as unlikely because the survival rates had been relatively stable or even slightly declining in the years before the trial. They called attention to the fact that in the years preceding institution of defibrillation by EMTs, relatively good survival rates were achieved under conditions where CPR was provided for an average of 5 minutes before the arrival of paramedics with defibrillating equipment.

Tab. 1. Summary of results from the study by Cobb et al

Group	CPR First	Standard	OR	p-value
<b>All (n)</b>	<b>478</b>	<b>639</b>		
ROSC	281 (59%)	340 (53%)	1.49	0.06
Discharged	142 (30%)	155 (24%)	1.66	0.04
< 4 min (n)	258	318		
ROSC	156 (61%)	186 (59%)	0.87	0.63
Discharged	82 (32%)	99 (31%)	0.70	0.87
≥ 4 min (n)	220	321		
ROSC	125 (57%)	154 (48%)	2.22	0.04
Discharged	60 (27%)	56 (17%)	7.42	< 0.007

### The trial by Wik et al

The only randomized trial to date comparing “CPR first” with “defibrillation first” was conducted in Oslo between June 1998 and May 2001 and included 200 patients, aged more than 18 years, with out-of-hospital VF or pulseless VT in whom ambulance personnel had not witnessed the cardiac arrest. After on-site randomization of patients meeting the above criteria, the victims were subjected to treatment according to either the guidelines of the European Resuscitation Council (10) with immediate defibrillation (standard group), or an experimental protocol in which 3 minutes of CPR was performed before attempting defibrillation for the first time and in which all subsequent CPR sessions were 3 minutes long regardless of rhythm (CPR first group). The main outcome variable was survival to hospital discharge. Secondary outcome variables were hospital admission with ROSC, 1-year survival, and neurological status at discharge and 1 year after discharge. Prior to data analysis it was decided that subgroups

with response times of up to 5 minutes or longer than 5 minutes were going to be analyzed in addition to the main analysis including all patients.

Results are summarized in Table 2. No difference between study groups was found in any of the main or secondary outcome variables when the entire study population was included in the analysis: survival rates to hospital discharge were 22% (23/104) in the CPR first group versus 15% (14/96) in the standard group,  $p = 0.17$ ; ROSC rates were 56% (58/104) vs 46% (44/96),  $p = 0.16$ ; 1-year survival rates were 20% (21/104) vs 15% (14/96),  $p = 0.30$ . There were no differences between the groups in neurological outcome either at hospital discharge or 1 year later.

In subgroup analysis, it was found that for the patients with response times longer than 5 minutes, the CPR first strategy appeared to give better results. Survival to hospital discharge rates improved from 4% (2/55) in the standard group to 22% (14/64) in the CPR first group,  $p = 0.006$ ; ROSC rates from 38% (21/55) to 58% (37/64),  $p = 0.04$ ; and 1-year survival rates from 4% (2/55) to 20% (13/64),  $p = 0.01$ . In the subgroup of patients with response times of 5 minutes or less, there were no differences in any of the main or secondary outcome variables. Regardless of response times, no difference in neurological outcome at hospital discharge or after 1 year was found in this study.

The authors concluded that there was no overall difference in survival for patients who received standard care vs CPR first before defibrillation, but for patients with ambulance response intervals of more than 5 minutes, rates of survival to hospital discharge and 1-year survival were higher in the CPR first group. They noted that similar to the results of Cobb et al, CPR first did not improve survival for the patient group with shorter response times, but pointed out that neither was survival worse. A remark was made that this could be due to a type II error and that a survival disadvantage could possibly have been found in a much larger trial with finer division of response times.

Table 2: Summary of results from the study by Wik et al

Group	CPR First	Standard	OR	p-value
<b>All (n)</b>	<b>104</b>	<b>96</b>		
ROSC	58 (56%)	44 (46%)	1.49	0.20
Discharged	23 (22%)	14 (15%)	1.66	0.20
1-year survival	21 (20%)	14 (15%)	1.48	0.35
≤ 5 min (n)	40	41		
ROSC	21 (52%)	23 (56%)	0.87	0.82
Discharged	9 (23%)	12 (29%)	0.70	0.61
1-year survival	8 (20%)	12 (29%)	0.60	0.44
> 5 min (n)	64	55		
ROSC	37 (58%)	21 (38%)	2.22	0.04
Discharged	14 (22%)	2 (4%)	7.42	0.006
1-year survival	13 (20%)	2 (4%)	6.76	0.01

The authors also proposed a mechanism for the beneficial effects observed in patients with response times in excess of 5 minutes treated with CPR first. It was stated that the basis for the worsened electrical and mechanical cardiac function in prolonged VF seems related to the relatively high metabolic requirements for VF, lack of oxygen supply, and an ultimate depletion of metabolic substrates and high-energy phosphate stores. The authors then hypothesized that CPR might produce sufficient cardiac perfusion to improve the metabolic state of the myocytes in such prolonged cases of VF, rendering the heart more susceptible to successful defibrillation.

The difficulty of defining the optimal duration of pre-defibrillation CPR was briefly discussed and it was stated that ideally the frequency spectrum of the electrocardiogram should be used to determine whether CPR should be started. The authors also noted that the concern that a higher rate of ROSC after prolonged cardiac arrest would produce more survivors with severe neurological damage did not occur.

#### **Methodological evaluation of the trials by Cobb et al and Wik et al**

The trial by Cobb et al was an externally controlled trial with a historical control group. Such a trial has some limitations that should be mentioned. First, the study and the intervention groups are separated in time. Therefore, changes in the study population with time have the potential to influence the results. Three studies suggesting that the incidence of VF is currently declining (2,11,12) raise concern that such a change may actually have taken place, and indeed, whereas the pre-intervention period accumulated patients at a rate of 15 per month, during the intervention period the average rate was only 13 patients per month. The mentioned studies hypothesize that the observed decrease in incidence may be due to a decreasing incidence and more effective management of coronary artery disease.

Second, although Cobb et al statistically adjusted for several differences between the patient groups, they did not examine or adjust for differences in the severity of the underlying cardiac disease (which may have changed based on the paragraph above), concurrent medical problems or behavioral risk factors.

Third, the person who was assessing neurological outcome from hospital records could probably not be blinded as to whether the patient was in the pre-intervention or the intervention period.

In addition, absence of randomization always leads to the concern that some unexpected confounding variables may be present.

The trial by Wik et al was a randomized trial, but a relatively small one. As a result, many of the relevant p-values were quite close to 0.05, which is regarded as the limit for significance. In the group of patients with response times of 5 minutes or less, slight non-significant worsening was seen in ROSC, survival

to hospital discharge, and 1-year survival rates. A larger trial may have had sufficient statistical power to show a significant difference.

The subgroup analysis has been criticized as essentially neutralizing the randomization scheme. However, the trial can still be considered as essentially a composition of 2 properly randomized trials, one including patients with response intervals of up to 5 minutes, the other including patients with longer response intervals. Also, it should be noted that in accordance with good research practice, the decision to analyze patients in subgroups was made prior to data analysis and was based on a logical hypothesis supported by previous research. The exact cut-off time of 5 minutes was chosen by the 2 main authors and communicated to the other authors, but not to any other study personnel. Thus the EMTs and paramedics did not know that patients would be separated at a 5-minute response time for purposes of analysis, although they may have known of the hypothesis that patients with longer response times would in general benefit most from the experimental treatment. Hospital personnel were blinded with regard to the treatment group. It can be concluded that methodologically the trial of Wik et al was of good quality and that splitting patients according to response times did not prevent randomization from carrying out its most important purpose of minimizing the possibility of unknown confounding variables affecting the results.

In summary, both trials have some shortcomings, but the fact that their results are so remarkably similar is an encouraging sign, as is the fact that the results are supported by several experimental animal studies.

#### **The 3-phase time dependent model of resuscitation ?**

Based on the evidence presented above, it would seem fairly certain that many patients with out-of-hospital cardiac arrest would benefit from a "CPR first" strategy. A 3-phase time sensitive model has been presented by Weisfeldt and Becker (14), describing what kind of treatment might be optimal for different lengths of cardiac arrest. The model distinguishes between 3 separate phases for the patient with VF, each with their own optimal treatment: the electrical phase, the circulatory phase, and the metabolic phase.

During the electrical phase, extending to approximately 4 minutes after the onset of VF, the optimal treatment is early defibrillation. To support this notion, the authors mention the success of the implantable cardioverter defibrillator (ICD), and many studies showing the efficacy of early defibrillation by e.g. police rescuers, casino security personnel, airport personnel or untrained members of the public are cited. According to current resuscitation guidelines, this strategy of early defibrillation is now applied to all patients regardless of the duration of VF. Still, most out-of-hospital cardiac arrests fall outside this category by the sheer time it takes to get a defibrillator to them.

During the circulatory phase, extending between approximately 4 and 10 minutes, the model proposes that the most important

initial therapy may be to provide limited circulation of blood with partial restoration of substrates including oxygen and washout of deleterious metabolic factors that have accumulated during ischemia. After thus optimizing the condition of the myocardium, defibrillation would then follow. In support of the notion of a circulatory phase, results from many experimental animal studies and the two human studies discussed above are cited.

The metabolic phase commences after approximately 10 minutes of circulatory arrest and is mostly outside the scope of this article, but for the sake of completeness a short description is presented. In this phase, both early defibrillation and a "CPR first" strategy quickly lose effectiveness and survival rates are poor. Global whole-body ischemia and reperfusion injury with widespread cytokine activity is speculated to be partly responsible, and studies where therapeutic hypothermia and controlled reperfusion with cardiopulmonary bypass have shown promise are cited.

The 3-phase model helps to conceptualize the process of treating VF and formulates important ideas and hypotheses that will have to be more closely investigated in future studies. However, thus far the data are too general to answer several important practical questions that need answers before purposeful changes can be implemented to the current resuscitation guidelines. Some of these questions are discussed below.

#### **How do we choose between CPR vs defibrillation first in practice?**

One major question that has to be answered in a manner relevant to practical field conditions is when to use a strategy of "CPR first" and when to defibrillate immediately. Both the trial by Cobb et al and the one by Wik et al showed no statistically significant worsening of survival in the patients with shorter response intervals. This could be used to argue that a strategy of "CPR first" be used for all patients regardless of how long VF has lasted. In the study by Wik et al, however, a slight non-significant worsening was seen in all outcome variables (Table 2), and as the authors noted, a larger study with finer subdivision of response times could have detected a survival disadvantage in the patient group with short response intervals. A further point to note is the fact that the ambulance response interval is only one part of the total ischaemic interval of the patient's heart. Thus, even in patients with the very shortest ambulance response times, VF may often have persisted for some time, making results of such studies unreliable when considering optimal treatment in cases of truly short lasting VF. This notion is supported by the fact that patients who receive prompt defibrillation within a minute or two, for example in special coronary care units, have excellent survival rates. In summary then, using CPR first always does not seem to be a sound strategy.

In many cases of out-of-hospital cardiac arrest, particularly when they have been witnessed and help has been promptly requested, ambulance response intervals may offer a relatively

accurate way to estimate the duration of VF. If a cut-off time to select between "CPR first" and "defibrillation first" strategies could be specified, it could then be used in such cases to select the optimal therapy. Wik et al hypothesized that the optimal cut-off time for "CPR first" vs "defibrillation first" may lie around a 4- to 5-minute response time but acknowledged the limitedness of their material with regard to making such estimates. Relevant animal studies (3-7) have used VF durations of 5-10 minutes as a model of prolonged VF. Of these, only one study (6) using 5 minutes of untreated VF showed a significant survival benefit for a "defibrillation first" strategy, suggesting that VF of shorter durations than this may be optimally treated by a defibrillation first approach. In a real-life situation however, any rigidly defined cut-off time seems unsatisfactory because of variation in the setting in which each case of VF is occurring. For example, some patients have received CPR from bystanders prior to the arrival of EMTs or paramedics, which has been shown to increase survival<sup>2</sup> and which can be expected to slow down the deterioration of the heart muscle and brain tissue. Also, people may have differing genetic and metabolic traits that make some people more resistant to damage by ischemia than others. Therefore, if possible, one would wish for a more case-specific way to choose between resuscitation strategies.

#### **Analyzing the ventricular fibrillation waveform (13)**

A promising method to analyze delays could arise from computerized signal analysis of the VF waveform. One method that has been cited by many investigators is frequency analysis of the VF waveform by a mathematical method called fast Fourier transforms (FFTs). By this method, the VF waveform can be separated into simpler component waves. The power of each component wave can then be plotted in a power histogram, and the frequency that divides the power histogram into two equal areas is called the median frequency (FM). FM has been shown to predict duration of VF accurately to within  $\pm 1.3$  minutes for the initial 10 minutes. The average error is  $\pm 0.86$  minutes. FM has also been shown to correlate with myocardial perfusion during external CPR. In one study involving swine, it was used to predict whether 1 of 3 defibrillation attempts would be successful with a sensitivity of 100% and specificity of 92.3%. Another study with swine showed that FM could still be used while CPR was in progress: after filtering the CPR artifacts, FM had a 100% specificity and sensitivity in detecting the successfully resuscitated animals. CPR has been shown to increase FM, and on the other hand, FM and thus the mathematically derived probability for a successful defibrillation have been shown to quickly deteriorate after CPR is stopped, for example to check for rhythm (16,17).

The problems with FM include the fact that human studies are scarce and interspecies variability has been pronounced in animal studies; some information in the VF waveform is lost because of the mathematical technique; collection of the ECG data segment needed for the analysis requires a few seconds. However, FM has been shown to be predictive of defibrillation success in out-of-hospital VF (18) and in a very highly specialized group of cardiac surgery patients (19), and

it is still the method that has been investigated the most. Other promising techniques are being researched which have many theoretical characteristics that could make them more practical to use than FM. For example, wavelet transformation analysis, perhaps the most promising new technique, does not lead to loss of information from the VF signal and would seem to be less affected by CPR artifacts of the ECG.

At present, no commercially produced devices offer the possibility to analyze VF in real-time. As more research using different signal analysis techniques to dissect usable information from the human VF waveform becomes available, this can probably be expected to change, and perhaps the future AEDs can verbally instruct their users when to defibrillate and when to continue CPR.

### Neurological consequences

Resuscitation of a patient in cardiac arrest constitutes a dramatic life-or-death situation that ends in either restoration of a perfusing cardiac rhythm or death. Therefore, it does not seem too surprising that when comparing effectiveness of different resuscitation techniques, rates of ROSC and survival to hospital discharge are often the variables that get most attention. The people involved in resuscitation efforts rarely see how the successfully resuscitated patient does in later life; for them, the definition of a successful resuscitation can therefore easily become achievement of ROSC and delivery of the patient to the hospital with stable vital signs. Sadly, many of the admitted patients do not survive to hospital discharge, and of those who survive, many have sustained at least some degree of neurological damage. As much as one would want to greet with joy any results that tell of increased survival rates for patients with cardiac arrest, the question of whether the increased survival rate comes at the cost of a greater risk of neurological debility seems justified.

Both human trials presented here did make an effort to evaluate neurological outcome in resuscitated patients: Cobb et al assessed neurological status at hospital discharge while Wik et al also tried to assess neurological status 1 year after the incident. The method of assessment used in both studies was through the Glasgow-Pittsburgh Outcome Categories (20), which distinguishes between 4 rough categories: category 1 includes patients with good performance and no disability, category 2 patients with moderate disability, category 3 patients with severe disability, and category 4 comatose patients. This scale has been criticized as too broad and not correlating well enough with more advanced methods of determining functional ability and quality of life like activities of daily living (ADL) questionnaires. The fact that no neurological disadvantage accompanied the greater survival rates observed in the studies by Cobb et al and Wik et al is encouraging, but in the future studies will be needed to evaluate neurological and functional ability more thoroughly and in a way that better reflects the patient's subjective view of quality of life.

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