Doing the Same Thing Over and Over, yet Expecting Different Results

Running title: Atkins; Doing the same thing

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The fundamentals of modern day CPR, compressions and ventilations, were first described in the 1950s and 1960s.\textsuperscript{1-3} The American Heart Association endorsed CPR in 1963 followed by the first publication of the Advanced Cardiac Life Support Guidelines 1974.\textsuperscript{4} Since then, there have been modest changes in the delivery of CPR, primarily recommendations for compression/ventilation ratios, compression depth, advanced life support measures with early defibrillation, airway management and pharmacologic therapies and improved organization of emergency response systems. Despite these changes, survival from out-of-hospital cardiac arrest remains poor, usually < 10%. The usual scenario is institution of CPR by bystanders or emergency medical system (EMS) providers, advanced life support provided at the scene, then transport to the closest emergency department. If return of spontaneous circulation (ROSC) does not occur, the patient is declared at the scene or the process is repeated by hospital personnel until a pre-determined time interval has passed and the patient declared dead.

Because of data demonstrating declining survival with increasing duration of CPR clinical decision rules guiding termination of resuscitation (TOR) in the field have been developed\textsuperscript{5, 6} and endorsed by professional organizations of EMS providers and adopted by many EMS systems. These allow EMS providers to terminate resuscitation prior to hospital arrival if there is no response to resuscitation efforts after a pre-determined interval, often 30 minutes. The rationale for these guidelines include prevention of intensive, futile care for hours or days, at great expense, and at best, extremely poor neurologic survival. Some feel, however, that such algorithms are self-fulfilling prophecies and may stifle progress.
Recently however, improvements in survival have been described as a result of technological advances and experimental investigation. Automated external defibrillators permit very early defibrillation and have led to improved out-of-hospital survival. Since the release of the 2005 AHA guidelines emphasizing compressions to improve cardiac output, modest improvements in survival have been documented. Greater survival has been noted with therapeutic hypothermia in the post cardiac arrest period. But despite these improvements, substantial increases in survival have not been observed.

In this issue of *Circulation*, Reynolds et al suggest that novel therapies should be evaluated earlier in the resuscitative efforts rather than after failure of prolonged traditional efforts. Using their local database developed from participation in the Resuscitation Outcomes Consortium Epistry, they examined survival to discharge from hospital stratified by functional outcomes relative to CPR duration. Favorable outcome was defined by modified Rankin score (mRS) of 0 (no disability) to 3 (moderate disability, but able to walk unassisted). Patients were also classified as unfavorable status (mRS 4-5, moderately severe to severe disability), ROSC without survival to hospital discharge and no ROSC (RS 6). CPR quality was measured by thoracic impedance or by an accelerometer placed on the patient’s chest. The time period studied, 2005-2011, coincides with the introduction and adoption of the 2005 guidelines emphasizing chest compressions and minimizing ventilations. Two models were constructed, one adjusted for prehospital covariates and the second adjusted for therapeutic hypothermia and cardiac catheterization. For those patients discharged with a mRS of 0-3, 90% had CPR durations of ≤16 minutes, for those discharged with mRS 4-5, CPR duration was 23 minutes and mRS 6 was 29 minutes. The dynamic probability of survival with a mRS of 0-3 is virtually a straight line.
down (from 6% to 2% survival) with a 0.5% decline in survival for each minute of CPR (my visual estimates of Figure 3). After 15 minutes of CPR duration, survival is 2% and remains unchanged thereafter. Adjusting for both pre-hospital and inpatient covariates, CPR duration was independently associated with favorable functional status at hospital discharge. Importantly, even after controlling for therapeutic hypothermia and cardiac catheterization, CPR duration remained an independent predictor of death or disability. The data they present are not new nor unexpected. Probability of survival to hospital discharge after out-of-hospital cardiac arrest with a mRS <3 declines rapidly with each minute of CPR. Current CPR strategies are effective in the initial 15 minutes and after that, are unproductive and often futile. The authors propose that novel therapies be implemented early in the resuscitation while meaningful survival is still possible.

These conclusions are somewhat in contrast to a related analysis recently published in Circulation comparing CPR duration to outcomes of pediatric in-hospital cardiac arrest using the in-hospital Get With the Guidelines-Resuscitation database. Median duration of CPR for survivors was 10 minutes and non-survivors 25 minutes, although, the proportion of survivors who received > 25-30 minutes of CPR is higher, especially for post-operative cardiac patients. The probability of a favorable outcome for all patients was < 20% at CPR durations of 20 minutes and declined to 10% at 40 minutes (visual assessment of Fig 2). However, the percentage of survivors to hospital discharge with good neurologic outcome following CPR durations of > 35 minutes varied from 44 to 68%, depending on pre-arrest diagnosis. The authors concluded that CPR for > 20 minutes was not futile in selected pediatric patients. The obvious difference between these studies is the patient population: i.e. pediatric vs adult and in-hospital
vs out-of-hospital. Yet a comparable adult study from the same in-patient database concluded that systematic increases in resuscitation duration could alter survival in a high-risk population.\textsuperscript{16}

In comparing these studies, one must remember that inpatient cardiac arrest is distinct from out-of-hospital and comparisons are likely not warranted.

Yet thinking that we can increase CPR duration to improve survival misses the point that more of the same will not result in dramatically improved outcomes for the majority of patients.

Prolonged resuscitation clearly predicts a higher probability of death. The experimental design of adding a therapy late in the resuscitation when end-organ damage is likely has failed to produce any change in outcome.\textsuperscript{17-19} The proposal of initiating investigational therapies early in the resuscitation has considerable merit. Do we wait to administer antibiotics until sepsis has occurred or when the infection is localized? Do we wait until metastatic disease is present before starting anti-cancer therapy? No. Any therapy is more likely to be effective when the process is not “widespread”. Given that cardiac arrest in any setting has a poor prognosis, implementing new therapies early in the resuscitation is justified.

But, along with developing novel therapies and an earlier paradigm for testing them, we need to consider additional investigative methods to the standard of randomized controlled trial.

Successful treatment of cardiac arrest requires a complex algorithm with integrated systems of care and it is difficult for single investigators or single sites to conduct these trials. The Resuscitation Outcomes Consortium has successfully built a large infrastructure across North America to conduct such trials. The Consortium has completed several controlled trials as well as 2 Phase II trials and multiple observational studies. Several more are in the design and early
implementation stage. Significant progress has been made in both the participating communities as well as within the broader resuscitation community. Most of the trials however involve modifications and adjustments in what can be considered standard therapy. This consortium provides an appropriate mechanism to test truly innovative CPR therapies while patients are still viable. Additionally, other models exist and should be exploited. Reynolds et al discuss the proposal by the Prague OHCA study group to use multiple aggressive efforts very early in the resuscitation. Another very successful “experimental” model has been exploited by the collaborative efforts of the University of Arizona and the Arizona Department of Health Services. Continuous quality improvement guided the changes in their protocols over a 10 year period. Initializing using chest-compression-only-CPR, which was not part of the American Heart Association guidelines, and aggressive post-resuscitation care statewide, they have dramatically increased the survival from out-of-hospital cardiac arrest.

Anecdotal reports and studies showing some good survival after prolonged resuscitation attempts are not evidence that prolonged CPR is adequate. The majority of patients have poor outcomes after 15 minutes. Rather, these unusual outcomes tell us there is more we don’t know and force us to ask what is different. Innovative thinking and experimental designs exploiting those differences to develop novel therapies may provide better resuscitation for all. Caution is warranted when developing TOR guidelines, especially for in hospital cardiac arrest, and the algorithms need to be continually re-evaluated in the light of new information. But, we critically need innovative hypotheses and therapies and experimental paradigms to test them before we can expect different results.

**Conflict of Interest Disclosures:** None.
References:


