Into the age of reanimation: promise and challenge in cardiac arrest care

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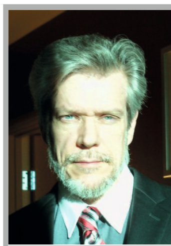

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Recent advances in cardiac arrest resuscitation, especially therapeutic hypothermia, have begun a paradigm shift in our approach to these patients, as underscored in the recent International Liaison Committee on Resuscitation guidelines [1]. The prospect of improved survival from cardiac arrest presents new clinical, scientific, political and ethical challenges. Foremost among these are the development and material support of effective clinical protocols, the funding and conduct of research to build upon recent advances, the re-evaluation of more intensive or invasive reperfusion strategies, and deciding which patients are likely (or not) to derive benefit from aggressive cardiocerebral resuscitation and post-resuscitation care. The approach to these problems mandates a constructive dialogue between clinicians, scientists, policymakers and the general public.

In this issue of *Therapy*, Sasson *et al.* provide a summary of the 2010 International Liaison Committee on Resuscitation guidelines [1]. The recommendations of the committee reflect dramatic changes in the approach to cardiac arrest and resuscitation, a paradigm shift that will have profound implications for clinical practice, research, healthcare economics and medical ethics. While recent advances in cardiac arrest resuscitation are cause for optimism, they present extraordinary challenges to providers, scientists, hospitals and the general public.

The past

Until recently, the prognosis for patients with cardiac arrest remained grim [2]. Novel therapies came and went like clothing fashions: pentobarbital, lidoflazine, high-dose epinephrine, abdominal-thoracic CPR, intra-arrest thrombolysis, machine-assisted CPR and free radical scavengers. None could be shown to improve neurologically-intact survival. Indeed, outcomes from cardiac arrest changed little in the second half of the 20th century [3]. We could achieve return of spontaneous circulation (ROSC) in many patients, but few would survive to hospital discharge, and of those who did, most had debilitating neurological damage [4].

Although the search for neuroprotectants and better reperfusion strategies continued, clinicians increasingly recognized that aggressive resuscitative measures that would restore circulation long enough to move the patient to the ICU were futile – or worse. Restoring circulation, after all, is the means, not the end. Emergency physicians, confronted by cardiac arrest patients with 'long down times' attempted resuscitation not out of any expectation of success, but in spite of it, and knew that the last thing such patients needed was a pulse [5].

Things are different now.

The present

A more aggressive attitude toward resuscitation from cardiac arrest is taking hold. The questions facing the resuscitologist in 2011 are quite different from those of a decade ago. We have seen renewed interest in the post-resuscitation period and a rush to clinical protocols that maximize neurological recovery in patients who attain ROSC. Most importantly, as reflected in the article by Sasson *et al.* and the International Liaison Committee on Resuscitation guidelines themselves, there is a sense that the stakes in cardiac arrest are higher [1]. The physician has a heightened sense of urgency about restoring circulation, initiation of therapeutic hypothermia and activation of the catheterization laboratory. Nothing succeeds like success.

Why this new-found optimism and urgency? It can be summed up in one word: hypothermia. This venerable therapy, used in reanimation

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attempts for millennia, and a documented technique in modern medical practice for nearly 200 years [6], had been abandoned because of technical constraints and side effects. Research into cerebral resuscitation focused instead on identifying mechanisms that could be targeted by pharmacological monotherapy [7]. A familiar pattern began to emerge: drugs that worked in rats or dogs, but failed miserably in clinical trials. Billions of dollars and millions of man-hours were spent. Confronted by the molecular complexity of ischemic brain injury, some, including ourselves, predicted that combination therapy, targeting two or more of the independently lethal processes, was our best chance for benefit [8].

In retrospect, it is clear we have had a viable neuroprotectant available for some time. One need only peruse the stroke and brain ischemia literature of the past three decades to see that exquisite attention was given to maintaining experimental animal preparations at physiologic temperatures [9], for it was well-recognized that hypothermia had a profound neuroprotective effect.

With the landmark trials published in the *New England Journal* in the first decade of the 21st century, therapeutic hypothermia reclaimed its central role in reanimation, and demonstrated that improvement in neurologic recovery after prolonged cardiac arrest was possible [10,11]. This remarkable advance mandates critical evaluation, for it is the foundation upon which we must build if we are to advance therapy for cardiac arrest. This evaluation must take place within the three interlocking arenas of research, clinical practice and public policy.

Hypothermia must remain a central focus of cardiac arrest and brain ischemia research. As Sasson *et al.* note, it is widely held that hypothermia exerts its neuroprotective effect by decreasing metabolic demand and the rate of biochemical reactions [1]. While metabolic and kinetic effects are certainly important, a growing body of data indicates that hypothermia modulates apoptotic and cell survival pathways [12,13]. A more complete understanding of hypothermia's neuroprotective effect at the molecular level may not only lead to refinements in the implementation of hypothermia itself, but can be expected to yield insights leading to the development of new therapies.

The clinical arena must accommodate itself to the new reality of cardiac arrest care, by providing the facilities, personnel and expertise necessary for implementation of more aggressive resuscitation and post-resuscitation care. As the review notes, there has been 'a lot of ink' spent on the need to establish resuscitation centers, but there is little conclusive evidence that regionalization of cardiac arrest care will be more cost-effective or yield improved outcomes. Can one extrapolate the outcome data from trauma centers and percutaneous coronary intervention hospitals to cardiac arrest patients? Will establishment of these centers be driven by evidence of effectiveness, by marketing or finances?

The public policy arena bears a heavy burden in all of this, for with the prospect of improved survival after cardiac arrest comes questions of compensation, public education, center certifications, care for populations geographically or socioeconomically removed from such centers, emergency medical services protocols and funding of critical research.

The future

Clearly, the future of resuscitology is more exciting, rigorous, sophisticated and expensive. Prolonged and costly resuscitations with lengthy post-resuscitation hospitalizations may become the norm. We can expect recent advances to spur the development of new, more expensive resuscitation strategies, and renew interest in old ones, such as open cardiac massage, heart–lung bypass and intra-arrest cardiac catheterization.

We will need newer and more reliable technologies to monitor the progress of resuscitation. Although some advocate a goal-directed therapeutic approach [14], there is already increased interest in monitoring the ultimate end organ, the brain. Technologies need to be studied that inform the resuscitologist of brain blood flow, oxygenation, metabolic status and ultimately neurological prognosis.

If hypothermia restores 49–55% of post-arrest patients to their former lives, it may seem reasonable to expect that a combination of hypothermia with novel neuroprotectants can increase those numbers to 60% or higher. Promising adjunct therapies include growth factors such as insulin, IGF1 and progesterone; and novel non-pharmacologic therapies such as enzymatic photomodulation. These therapies will add to the complexity and cost of post-resuscitation care.

The foregoing challenges are difficult and complex, but they pale in comparison to the greatest dilemma facing us in the age of cardiocerebral resuscitation: who should be resuscitated? As we go forward, we must remember two important facts: first, that our healthcare systems are being crippled by exorbitant and unsustainable costs, with most of those costs incurred at the end of life; and second, that cardiac arrest happens to everybody.

As we enter the era of reanimation, it is critical that clinicians, scientists, policy makers and the public come squarely to terms with the brutal reality that not everybody can, or should be, reanimated. Recent advances in resuscitology, and those that are to come, will confer great benefits on humanity. However, the price tag will be high, and part of that price must be a definitive and final recognition that the two prime duties of the physician, the preservation of life and the relief of suffering, do not always go hand-in-hand.

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