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## Critical Care and Emergency Medicine

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## Critical Care and Emergency Medicine

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The emergency department (ED) and intensive care unit (ICU) are the frontlines in the battle against stroke. It has become increasingly clear that the efficacy of stroke therapy depends first and foremost on early intervention. However, this demanding race against time has overwhelmed many hospitals and emergency departments, creating new demands for rapid patient triage, imaging and monitoring that simply cannot be met. In 2006 a landmark study commissioned by the Institute of Medicine entitled "Hospital-Based Emergency Care: At the Breaking Point" detailed how understaffing, overcrowding, lack of resources and difficulties in obtaining specialist coverage have created a crisis in our emergency rooms.<sup>1</sup> How to successfully integrate a new paradigm of ultra-emergent stroke care into this environment is a major challenge that will confront our field over the next decade.

Realizing that the very feasibility of acute stroke therapy depends on well-coordinated emergency care, a growing body of research has focused on designing more efficient methods for delivering acute stroke therapy to as many people as possible, as quickly as possible. At the same time, despite a growing literature documenting that victims of life-threatening neurological disease such as intracerebral hemorrhage and traumatic brain injury have better outcomes when cared for in dedicated neurological ICUs,<sup>2-5</sup> a consensus statement by the Brain Attack Coalition on standards for Comprehensive Stroke Centers identified neurointensivists and dedicated neuro-ICUs as desirable, but optional.<sup>6</sup> This likely speaks much more to practical considerations regarding the physician workforce and existing hospital infrastructures than what is truly best for patient care.<sup>7</sup>

### Emergency Stroke Care

In 2006 a number of reports focused on the efficacy of various interventions designed to facilitate acute stroke care and speed up the time to perform imaging and therapeutic interventions. All of these studies involved collaboration between multiple disciplines and uniform management protocols. In one of the most strikingly positive studies, Lindsberg and colleagues in Finland moved their CT scanner to the ED and instituted a protocol for routine prehospital notification of the stroke team, essentially moving the triage step to the prehospital phase. The door-to-CT interval dropped from slightly over 1 hour to just 7 minutes, and access to thrombolysis at their institution increased from only 23

patients in 1999 to 100 patients in 2004 and 183 patients in 2005.<sup>8</sup> A telestroke service established in Germany in 2003 connecting 5 community hospitals to 2 academic medical centers demonstrated improved outcomes when compared with 5 similar community hospitals without access to tele-medical support. Of 3122 stroke patients treated overall, not only were all indicators of the quality of acute stroke care met more often in the 5 telestroke hospitals, but the frequency of death or moderate-to-severe disability was also significantly reduced (44% versus 54%;  $P < 0.0001$ ).<sup>9</sup> At the University of Texas in Houston, Wojner-Alexandrov and colleagues found that a multilevel educational program directed at emergency medical services resulted in only modest improvements in the proportion of stroke patients arriving within 2 hours of onset, and in the frequency of IV thrombolytic therapy.<sup>10</sup> These results suggest that educational efforts need to be combined with protocols that redirect provider behavior in order to get significant results.

Although the implementation of ED-based stroke protocols can potentially improve response times and outcomes after patients arrive at the ED, it has become increasingly apparent that the biggest impediments to rapid stroke intervention exist during the prehospital phase. Kleindorfer and colleagues analyzed 978 stroke patients in Cincinnati and found that only 38% called 9-1-1 to activate emergency medical services, which is the most powerful potentially modifiable determinant of reduced onset-to-treatment times in stroke care.<sup>11</sup> In the 4-state Paul Coverdell National Acute Stroke Registry, only 20% to 25% of stroke or transient ischemic attack patients arrived to the ED within 3 hours of symptom onset, and the frequency of IV thrombolysis ranged from 3.0% to 8.7%. Only with a massive public education effort focused on the importance of recognizing early stroke symptom and activating emergency medical services can this problem be solved.<sup>12</sup>

### Rapid Neuroimaging

As high speed, multislice, helical CT scanners have become more common, many stroke centers have adopted the routine use of CT perfusion and angiography (CTP/CTA) in the ED for all patients with suspected stroke. Despite the theoretical attractiveness of emergency MRI to detect perfusion-diffusion mismatch, the longer time required to perform these studies (45 to 60 versus 15 to 30 minutes) and issues of

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practicality have hindered widespread use. By contrast, CT scanners are ubiquitous, and often physically located within the ED and staffed to run 24 hours a day. At the University of San Francisco, Smith and colleagues have shown that after screening out patients with potential baseline kidney disease using a simple clinical checklist, routine CTA/CTP using a 400 mL contrast bolus can deliver high-resolution images of brain perfusion images and the entire cerebrovascular axis from the aortic arch to the intracranial vessels with a median scanning time of 22 minutes.<sup>13</sup> This protocol has been shown to be safe, leading to minor creatinine elevation ( $>0.5$  mg/dL) in  $\approx 5\%$  and frank renal failure in 0.37%.<sup>14</sup> The detection of proximal middle cerebral artery occlusion at a mean of 180 minutes after onset has since been validated to be an independent determinant of death or disability.<sup>15</sup> Many centers are finding the routine application of CTA invaluable for selecting patients for primary or “bridging” intra-arterial therapy. With improved image analysis techniques, quantitative CTP imaging can also guide treatment decisions by mapping the extent of tissue at risk,<sup>16</sup> and may also be able to identify salvageable from unsalvageable penumbral brain tissue.<sup>17</sup>

### Cardiac Arrest

In our view one of the most important stories in the emergency management of stroke is actually a nonstory: namely, how *little* progress has been made in the widespread application of hypothermia for global hypoxic-ischemic brain injury. Imagine that your spouse or child experiences the unthinkable—an out-of-hospital cardiac arrest. The good news is that the event is witnessed, bystander CPR is initiated promptly, and that your loved one is successfully defibrillated by emergency medical services within 15 minutes. The bad news is that your loved one is now comatose, has doubtlessly experienced some degree of damage to the brain, and is now actively experiencing reperfusion injury.

Although it is not traditionally considered the purview of stroke specialists, global hypoxic-ischemic injury is undeniably nothing less than the world’s worst form of stroke. Historically, only 15% of patients who are successfully resuscitated after out-of-hospital cardiac arrest leave the hospital alive. Remarkably, despite these terrible odds, in 2002 two randomized controlled trials demonstrated that induced hypothermia to a target temperature of 33°C for a duration of 12 to 24 hours results in a 40% increase in the odds of eventual survival with a good functional outcome at 6 months (55% versus 39%;  $P=0.009$ ). Yet the reality is that at least in the United States, in the hypothetical scenario above your comatose and acutely brain-injured spouse is almost certainly *not* going to be cooled and given the best possible chance for recovery.<sup>18,19</sup> For a variety of reasons, therapeutic hypothermia for cardiac arrest has been slow to catch on.

In 2006 Merchant and colleagues reported an international internet-based survey of 2248 critical care, cardiology, and emergency medicine specialists who care for cardiac arrest victims to learn more about their practices and attitudes regarding hypothermia.<sup>20</sup> The vast majority (74% of US respondents) had never used hypothermia for this indication.

The most frequently cited reasons for nonuse by respondents were “not enough data,” “not part of Advanced Cardiac Life Support guidelines,” and “too technically difficult to use.” Other unstated reasons might include the shroud of therapeutic nihilism that has traditionally surrounded hypoxic-ischemic coma, the novelty and unfamiliarity of cooling technology, the requirement of multidisciplinary care teams (ie, emergency medicine, cardiology, neurology) to provide this treatment, and the lack of precedent for treating this form of brain injury as a medical emergency.

Given the tremendous unmet need and the fact that the typical level of evidence for establishing a standard of care—two randomized controlled trials—has already been met, it seems questionable whether more trials are needed to justify the widespread implementation of hypothermia treatment protocols. Rather, more effort should be made to provide education, training, equipment and treatment pathways to the multidisciplinary provider teams that are motivated to use this new and unfamiliar therapeutic modality. Active involvement of the stroke community, including the incorporation of cardiac arrest protocols into the care plans of comprehensive stroke centers, is one way to potentially increase the availability of this treatment.

### Decompressive Hemicraniectomy

Decompressive surgery for malignant middle cerebral artery territory infarction is still a controversial issue in neurology and neurosurgery. Over the past decades, several case reports and smaller retrospective case series have suggested that decompressive surgery is possible treatment option for massive hemispheric stroke. However, no controlled data has been available to support its use. It was not until 1995 that a large prospective case series of patients treated with hemicraniectomy was published.<sup>21</sup> This series also included a concurrent control group, which, sadly enough, was not a randomized control group. Nevertheless, in this control group the well-known 80% mortality with maximum conservative treatment was demonstrated, whereas the mortality rate in the surgically treated group was only 34%. Among the survivors, the quality of survival was surprisingly good with a mean modified Rankin Scale score of 2.6. Unfortunately, comparison of these mortality rates is confounded by the fact that the controls were significantly older and were treated up to 8 years earlier than the hemicraniectomy group. Thus, there may have been shifts in general ICU practice that may also account for the observed difference in mortality.

Fortunately more data are on the way. As of 2006, five randomized trials have been designed to investigate the efficacy of decompressive surgery: The Hemicraniectomy And Durotomy On Deterioration From Infarction Related Swelling Trial (HeADDFIRST) randomized 26 patients between 2000 and 2003.<sup>22</sup> A nonsignificant reduction in mortality was reported. The final results, however, have not been published yet. Between 2001 and 2004 four other studies were initiated: One in the Philippines called Hemicraniectomy For Malignant Middle Cerebral Artery Infarcts (HeMMI), and three European trials called Hemicraniectomy After Middle cerebral artery infarction with Life-threatening

Edema Trial (HAMLET) in the Netherlands, DEcompressive Craniectomy In MALignant middle cerebral artery infarcts (DECIMAL) in France, and DEcompressive Surgery for the Treatment of malignant INfarction of the middle cerebral artery (DESTINY) in Germany.<sup>23</sup>

Beyond mere survival, the relevant question in these studies is the long-term functional outcome of patients treated with hemicraniectomy. The concern of many clinicians has always been that a reduction in mortality might be outweighed by a major disability in most survivors, leaving most patients severely disabled and facing a life of dependency, pain, and hopelessness. Thus, the primary end point in DESTINY is not mortality, but rather functional outcome according to the modified Rankin Scale after 6 months. Assessments of quality-of-life will also be performed in the ongoing hemicraniectomy trials.

### Blood Glucose Control

Poststroke hyperglycemia is a common and well-documented phenomenon, and hyperglycemia has been implicated as a risk factor for poor outcome as well as an important determinant of hemorrhagic infarction after thrombolytic therapy.<sup>24</sup> In 2001, Van den Berghe and colleagues published a landmark clinical trial demonstrating that intensive insulin therapy focused on maintaining tight normoglycemic control significantly reduces the mortality of surgical ICU patients.<sup>25</sup> As a result, continuous insulin infusion has become a standard of care for critically ill patients of all types around the world. However, there has never been much data specifically evaluating the risks and benefits of insulin infusion therapy in neurological patients. In early 2006 Van den Berghe published an intriguing sub-group analysis of neurological patients in the surgical ICU study population.<sup>26</sup> Intensive insulin therapy prevented secondary injury of both the peripheral and central nervous system and was associated with significantly improved functional outcome. This was mediated in part by significant reductions in intracranial pressure, seizures, and critical illness polyneuropathy and hence ventilator dependence.<sup>26</sup>

More data on tight glycemic control emerged in 2006 with the results of a follow-up 1200 subject trial in medical ICU patients.<sup>27</sup> In this study mortality was not reduced, but the intensive insulin group experienced significantly fewer ICU complications, including less renal failure and a reduction in the duration of mechanical ventilation. Although these data are not as robust as the initial study in surgical ICU patients, this trial still suggests that tight glycemic control is worth pursuing in critically ill stroke patients with respiratory failure or multisystem organ failure. Hyperglycemia induces a pro-oxidative and proinflammatory state that can cause direct neuronal toxicity and a procoagulant state. Additional trials are underway to determine whether insulin infusion therapy has a role in improving neurological outcome in noncritically ill patients with moderate-to-severe nonlacunar stroke.

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