

## Procrustes, the Traumatic Penumbra, and Perfusion Pressure Targets in Closed Head Injury

THE cerebral perfusion pressure (CPP; mean arterial pressure—intracranial pressure) is a major determinant of cerebral perfusion in the injured brain. Several recent studies have attempted to provide data on optimal CPP targets within the context of protocols for the intensive care management of severe traumatic brain injury. The report by Nordström *et al.*<sup>1</sup> in this issue of ANESTHESIOLOGY adds to our information on this subject. Many centers use an approach based on a conceptual framework popularized by Rosner *et al.*<sup>2</sup> and attempt to keep CPP above the lower limit of cerebrovascular autoregulation, which is thought to be shifted upwards following traumatic brain injury. This view has significantly influenced current thinking on this topic, and recent expert guidelines<sup>3</sup> have suggested that CPP be maintained above 70 mmHg. However, a different approach, first proposed by clinicians from Lund, Sweden,<sup>4</sup> is based on interventions aimed at reducing intracranial volume and, hence, intracranial pressure. Perhaps the largest perceived difference between the Lund approach and the Rosner *et al.*<sup>2</sup> approach (and CPP targets of 70 mmHg specified in current published guidelines) is the stated willingness of the Lund group to accept CPP targets as low as 50 mmHg.

Although both of these approaches have been shown to result in good clinical outcomes,<sup>2,5</sup> they have never been directly compared. However, a recent randomized study by Robertson *et al.*<sup>6</sup> found no benefit, in terms of the Glasgow Outcome Score, from CPP-targeted therapy (aimed at maintaining CPP above 70 mmHg) when compared with conventional intracranial pressure-targeted therapy (in which CPP was maintained above 50 mmHg). This result was attributed, at least in part, to increased cardiorespiratory complications of therapy in the CPP-targeted group. A recent commentary by Robertson<sup>7</sup> in ANESTHESIOLOGY made a persuasive case for targeting a CPP of 60 mmHg in traumatic brain injury protocols. These results provide useful guidance on optimal CPP levels across patient populations. However, they do not address the issue of heterogeneity between or within patients, which could result in some patients, or some

areas in the injured brain, benefiting from a higher (or lower) CPP. Such optimization could conceivably result in subtle improvements in neurocognitive outcome that might be missed by the Glasgow Outcome Score.

Nordström *et al.*<sup>1</sup> attempt to address the first of these two issues in their report. They used microdialysis to monitor extracellular fluid metabolite concentrations from perilesional (“worse”) tissue and relatively normal (“better”) tissue in 50 patients with head injury and retrospectively investigated the relationship between CPP and extracellular fluid concentrations of lactate, pyruvate, and glucose. Extracellular fluid glucose concentrations were unrelated to sampling site and were unaffected by CPP levels. However, extracellular fluid lactate concentrations were higher in worse areas than in better areas when the CPP was greater than 70 mmHg or less than 50 mmHg. Although lactate concentrations in better areas did not vary significantly with CPP, lactate concentrations in the worse areas were significantly higher when CPP decreased to less than 50 mmHg. Lactate-pyruvate ratios generally followed these trends, but differences were less robust. The authors infer that perilesional tissues are more sensitive than normal brain tissue to reductions in CPP and do not tolerate CPP levels below 50 mmHg. They also interpret these data to support the use of the Lund protocol, with reductions in CPP to 50 mmHg if needed for intracranial pressure control.

While these results are interesting, we need to consider several issues. Clinical management in these patients was based on the Lund concept.<sup>4,5</sup> Although CPP was initially maintained at 60–70 mmHg, it was allowed to drop to 50 mmHg if this allowed control of intracranial pressure. Most patients received low-dose thiopental (0.5–3 mg · kg<sup>-1</sup> · h<sup>-1</sup>) and antihypertensives (metoprolol and clonidine); 11 received dihydroergotamine to reduce cerebral blood volume. These treatment modalities and the variable (but unspecified) levels of hyperventilation that the patients received represent important confounding factors that may have been responsible, at least in part, for some of the metabolic abnormalities seen. Thus, the patients with the lowest CPP values may well have been the ones who received dihydroergotamine for intracranial pressure control or were hyperventilated to moderate hypocapnia—interventions that have either the potential<sup>8</sup> or the documented effect of reducing regional perfusion<sup>9</sup> and causing metabolic deterioration.<sup>10</sup> It is also important to point out that lactate concentrations in the worse areas were significantly higher than those in the better areas, even when the CPP was greater than

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70 mmHg. The investigators did not explore the possibility that further increases in CPP might normalize lactate concentrations, even in perilesional regions. Finally, they did not provide information on how these intermediate physiologic end points were related to eventual clinical outcome. While the data they present do advance our understanding of pathophysiology, relating these data to local or global outcome would be an important step in establishing the role of microdialysis as a clinical monitoring tool.

Despite these caveats, the results of the study conducted by Nordström *et al.*<sup>1</sup> are important because they highlight differences in pathophysiology within the injured brain and show that changes in physiology may have selective effects in vulnerable perilesional areas. This raises the possibility that we may have to tailor critical care management to prevent extension of injury to such areas. The *ischemic penumbra* is a concept that has long been recognized in experimental<sup>11</sup> and clinical stroke<sup>12</sup> and represents a region of tissue that is most affected by clinical management and neuroprotective interventions. These data, along with those provided by physiologic imaging studies,<sup>9,13</sup> make a strong case for identifying these perilesional areas as a *traumatic penumbra*, in which we can do the most harm or good depending on how we manage patients. Such perilesional areas are often in the vicinity of frontal and temporal contusions, in regions that have important roles in memory and executive performance.<sup>14–16</sup> Since much of the brain is at risk for secondary injury from physiologic insults following brain trauma, the traumatic penumbra may need to be defined physiologically rather than confined in terms of perilesional anatomy. However, regardless of the location of such tissue, improvements in outcome produced by preservation of neuronal function in these areas may be of immense importance to patients but may not result in movement along a relatively coarse, five-point Glasgow Outcome Score. Benefits from such targeted interventions will therefore need to be assessed by outcome measures with better discrimination at the higher end of the outcome spectrum; formal neuropsychologic assessment may be needed, but the extended Glasgow Outcome Score<sup>17</sup> is a useful step in this direction.

Finally, Nordström *et al.*<sup>1</sup> may have missed an important opportunity. In an effort to assess the effect of regional pathology on local physiology, they ignored interindividual variations in their analysis and pooled data from different subjects within CPP ranges. It would have been interesting to know whether the inflection point for elevation of lactate concentrations with reductions in CPP varied between patients, allowing individual optimization of CPP values. Such variability would not be unexpected. There are good data now to show that individual patients may possess different optimal ranges of CPP for autoregulatory efficiency,<sup>18</sup> and that patho-

physiology can change within patients over time.<sup>19</sup> At a more fundamental level, we know that genotype can modulate outcome in head injury,<sup>20</sup> although the pathophysiologic mechanisms by which such modulation occurs remain unclear.

Greek mythology tells of an innkeeper named Procrustes (or “one who stretches”), a robber in the myth of Theseus who preyed on travelers along the road to Athens. He offered his victims hospitality on a magical bed that would fit any guest. He then either stretched the guests or cut off their limbs to make them fit perfectly into the bed. Our attempts to find a unitary CPP value that fits all parts of the brain in all patients may represent a Procrustean approach, the time for which has passed. We need to try to move away from attitudes that try to shoehorn patients into a single range of CPP values, either at the lower or higher end of the spectrum of discussion (or argument!). The data from Nordström *et al.*<sup>1</sup> add to the growing evidence of pathophysiologic heterogeneity between and within patients following head injury and provide support for the concept of a traumatic penumbra. The challenge is to find ways to identify such penumbral tissue, to define management approaches that best preserve it in individual patients, and to find sensitive measures that can determine whether such individualized therapy results in significant clinical benefit.

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## Getting Older Is Not Necessarily Getting Better

SOME things improve with age. Vintage wine, firewood, and one's memory of past triumphs come to mind. Unfortunately, stored blood is not among them. Blood preservative solutions were developed to eliminate reliance on vein-to-vein transfusion and to improve blood supply and logistics.<sup>1</sup> No one expected that, at the end of several weeks of refrigerated storage, blood cells would perform exactly as they do when they exit the donor's vein. Small compromises in erythrocyte quality and quantity, commonly referred to as the *storage lesion*, are tolerated as the price of increased blood availability. However, clinicians do not expect this price to include harm to their patients. In this issue of ANESTHESIOLOGY, Leal-Noval *et al.*<sup>2</sup> add their caution to a lingering suspicion that something in stored allogeneic erythrocytes may increase morbidity in surgical patients. How legitimate is the concern that prolonged storage is the culprit?

Freshly collected erythrocytes lack a nucleus, mitochondria, the ability to divide, and the capacity to synthesize nucleotides and proteins. In the refrigerator, the cells age somewhat less gracefully than they do *in vivo*. The erythrocyte's metabolic machinery declines progressively during storage, and a number of biochemical and biomechanical changes occur that affect survival and function.<sup>3</sup> Membrane loss by microvesiculation alters its lipid composition. With membrane loss comes some decrease in the flexibility that allows the cell to transit the microcirculation and exchange gases efficiently. Loss of membrane proteins and a shift to glycolysis make the

erythrocyte more vulnerable to oxidative stress and lipid peroxidation. When stored in the presence of leukocytes, erythrocytes leak potassium, and increased hemolysis is observed. Histamines, lipids, cytokines, and a variety of other substances accumulate in the supernatant solution in a time-dependent manner. The organic plasticizer di(2-ethylhexyl)phthalate migrates from the blood bag into the erythrocyte lipid membrane. Additional manipulations, such as filtration and gamma irradiation, prior to transfusion may further modify the cells. The clinical importance of these aggregate changes is unknown.

A better understanding of erythrocyte biochemistry and the additives that influence it, as well as a bit of luck and serendipity, have resulted in preservatives and containers that have increased the storage interval progressively. In 1914, blood could be stored for no more than 6 days. Today, it is refrigerated for up to 6 weeks. Efforts to further extend erythrocyte shelf life continue as we try to conserve a dwindling margin of safety in blood supplies.<sup>4</sup> Yet as newer preservative solutions are developed, the clinical effects of prolonging blood cell storage are investigated only obliquely. We lack good scientific assays of erythrocyte transfusion efficacy *in vivo*. One surrogate measure, 2,3-diphosphoglycerate, becomes undetectable by the end of storage, leading to reduced oxygen offloading ability for 12-48 h posttransfusion. The clinical impact of this loss has been difficult to demonstrate. Adenosine triphosphate, the accepted surrogate assay for erythrocyte viability, turns out to be a poor predictor of *in vivo* circulation. The gold standard for viability remains survival of 75% of injected radiolabeled erythrocytes at 24 h, an arbitrary standard that tolerates up to a quarter of nonviable erythrocytes transfused at the end of storage. However, until compelling evidence that these changes affect transfusion outcomes emerges, research to extend storage will inevitably trump efforts to improve erythrocyte quality.

How do these findings relate to the report of Leal-Noval *et al.*<sup>2</sup>? Numerous observational studies using multivariate analysis models have suggested that allogeneic

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erythrocyte transfusions have unexpected adverse effects, such as enhancing cancer recurrence and susceptibility to postoperative infections, an association that has come to be called *transfusion-related immunomodulation*.<sup>5</sup> Controlled clinical trials and meta-analyses have been less convincing.<sup>6-8</sup> Nevertheless, several candidate mechanisms for transfusion-related immunomodulation have been proposed, and the length of erythrocyte storage numbers among them.<sup>9</sup> In addition, a small number of observational studies of different patient populations have demonstrated a statistical association between prolonged storage of allogeneic blood and (1) rate of infection in trauma patients, (2) mortality in the intensive care unit, and (3) postoperative pneumonia in open-heart surgery patients.<sup>9-11</sup> Each of these studies suffers from limitations in size, design, or methodology. In a retrospective analysis of 416 open-heart surgery patients, Vamvakas and Carven<sup>12</sup> reported that the mean length of storage of all erythrocyte units and the mean length of storage of the two oldest blood components were associated with postoperative pneumonia and infection. The findings of Leal-Noval *et al.*,<sup>2</sup> although similar, are neither identical nor comparable. Their prospective study of 897 consecutive patients undergoing open-heart surgery shows an association between the oldest stored unit (> 28 days) and nosocomial pneumonia. No relationship was found with the mean length of component storage. Both studies used highly sophisticated, although different, statistical techniques to deal with the multiple confounding variables. Vamvakas and Carven<sup>12</sup> included in their analysis, and accounted for, leukoreduced blood, leukoreplete blood, and combinations of autologous and allogeneic blood, as well as platelet and cryoprecipitate transfusions. Leal-Noval *et al.*<sup>2</sup> used buffy coat-poor erythrocytes in a different preservative and excluded from analysis patients who received autologous blood, as well as children younger than 16 yr, patients with preoperative fever or infection, those with anemia (hemoglobin < 11 g/dl), and those who died within 48 h of surgery. While there are good reasons for each of these decisions, they do make interpretation and comparison problematic.

Observational studies serve the purpose of posing questions. Even a cursory reading of the several referenced studies that involve numerous confounding variables—disease state, patient demographics, nature and number of the blood components, concurrent treatments, and definition of adverse events—suggests that additional observational studies will not answer this question. No clinical study is better than its controls, regardless of the statistical legerdemain that is used.

While the concern expressed by Leal-Noval *et al.*<sup>2</sup> that prolonged storage may be a risk factor appears reasonable, their assertion that a randomized, controlled trial would not be ethically defensible is premature. There is insufficient scientific evidence to change practice and discard erythrocytes stored for longer than 28 days (or 14 or 21 days, as suggested in the other studies), a change that would have a huge impact on how transfusion services are delivered. Simply put, in the case of erythrocyte storage, we need to know whether and how much age matters.

Evidence that blood transfusions work remains largely empiric. Large-scale clinical trials of erythrocyte safety and efficacy are not currently required prior to extending the storage interval, nor would such studies likely be useful or practical. However, once observational studies suggest that stored blood is harmful, carefully controlled, hypothesis-driven, prospective trials to confirm or refute the results become imperative. In this case, we need to determine whether some storage lesion contributes to posttransfusion pneumonia, infection in trauma patients, or mortality in the critically ill. If a clinically significant effect is confirmed in any of these settings, we need to determine why it occurs and how to prevent it.

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