In our recent large study of normobaric hyperoxia in traumatic brain injury (TBI), the data suggested the need for early and prolonged O2 treatment in patients with severe TBI. This observation was further supported by the lack of cerebral microdialysate changes after the application of normobaric hyperoxia treatment more than 48 hours postinjury in the study by Magnoni et al., as well as the recent work of Stiefel et al., who demonstrated improved survival in patients with TBI by using higher inspired O2 concentrations for a prolonged period.

Although Diringer and colleagues succeeded in completing their measurements in the first 24 hours after injury, they chose to apply normobaric hyperoxia treatment for only 1 hour before performing the second PET. In our study we saw no significant changes in the overall mean cerebral microdialysate glucose and lactate levels in the first few hours after initiating normobaric hyperoxia treatment. Of course, individual responses may vary (reflecting the diversity and extent of injury), but we believe that Diringer and colleagues’ conclusion—that normobaric hyperoxia had no effect in their study—is flawed because only 1 hour of treatment was used.

Traumatic brain injury is a multifaceted entity with an array of pathomechanisms that vary in extent and severity. Both the pathomechanisms and the variations may have contributed to the failure of the neuroprotection trials of the 1980s. The metabolic effects of brain injury are not easily demonstrated and are by no means fully understood. We tabulated the results of a review of the recently published evidence, in humans, with regard to normobaric hyperoxia in severe TBI (Table 1). All but 2 of these studies support the benefits of normobaric hyperoxia as a treatment option. In stroke, early treatment with normobaric hyperoxia has also led to improvement in imaging-demonstrated and clinical outcomes. Moreover, we have recently shown that early hyperbaric O2 therapy increases cerebral adenosine 5'-triphosphate (ATP) production in rats following lateral fluid-percussion injury, offering strong mechanistic support for an O2 delivery hypothesis in TBI. Interestingly, normobaric hyperoxia in the same experimental setting resulted in even higher levels of cerebral ATP.

Further mechanistic evidence of a causative role for mitochondrial impairment in TBI was recently shown using 1H-MR spectroscopy to detect N-acetylaspartate (NAA), a surrogate marker of neuron-specific mitochondrial impairment. Interestingly, 1H-MR spectroscopy revealed areas of reduced NAA within brain tissue peripherally to the contusion or traumatic lesion, which were not detected on CT, thus suggesting that the beneficial effects of hyperoxia therapy are likely to have a more potent effect on these perilesional areas. In yet another study, these hypoperfused perilesional areas were shown to have increased brain tissue PO2 to a lesser degree when compared with areas of unimpaired regional cerebral blood flow (CBF). In other words, perilesional neurons have increased vulnerability to mitochondrial impairment, and...
attempts to augment regional CBF and oxygenation of this tissue may be especially beneficial as long as the hyperoxia therapy is not prolonged to such an extent that it degrades the pulmonary status due to resorption atelectasis. Based on the evidence supporting increased perilesional susceptibility to the effects of hyperoxia therapy, authors in Cambridge, United Kingdom, using 15O-PET, cerebral metabolic rate of O2 (CMRO2) and brain tissue PO2. It was the use of a “pixel-based” regional assessment of contrast to Diringer and colleagues’ findings. The use of hyperoxia seemed to significantly reduce the volume of “tissue at risk for ischemic damage”—by as much as 100 ml in certain patients. Note, however, that the observed benefit was independent of changes in microdialysates and global 13O-PET changes, suggesting additional, as yet undetermined, mechanisms.

Finally, the recent emergence of cortical spreading depression (CSD) as a major factor that causes worsening of delayed ischemic damage in the injured human brain may offer both an alternative explanation for the diversity of responses in human brain injury and the possibility of potential treatments hitherto not appreciated. Along these lines, experimental evidence seems to suggest that local tissue hypoxia associated with CSD is caused by a transient increase in O2 demand that exceeds the local vascular O2 supply. Normobaric hyperoxia may thus provide an exciting new treatment modality under these circumstances as it may limit or even inhibit these spreading phenomena and accompanying ischemic effects.

We believe that normobaric hyperoxia may offer a simple, minimally invasive, and easily applicable adjunct in the early management of TBI. Furthermore, the accumulation of evidence strongly supports the call for a phase II or III multicenter trial to investigate the effects and outcome of such an intervention in patients with severe TBI.