

results are that groups providing noise, both PAV and noisy PSV, had a reduced venous admixture and improved oxygenation after 6 hrs, compared with animals receiving PSV. Although this study was designed to match groups on TV (6 mL/kg), inspiratory effort was higher in the PAV group. The characteristics of noise (i.e., the pattern of TV variation) differed between the modes, but both provided a sufficient coefficient of variation to improve oxygenation. One limitation is the small severity of the lung injury as reflected by the high P_{aO_2}/F_{iO_2} ratio and the weak histological-damage score. Furthermore, the lung inflammatory markers were probably not sufficiently increased to detect any variations between groups.

So, what does this study add to the field? First, whatever the source of noise, external or intrinsic, both modes provide adequate alveolar ventilation and improve precociously oxygenation. However, higher inspiratory effort is needed with PAV. Whether noisy PSV further unloads respiratory muscles for the same work needs to be clarified. Secondly, the impact of noisy ventilation on lung inflammation is still unknown. Only one study involving biologically variable ventilation has observed lower tracheal interleukin-8 expression (5). Finally, more attention should be paid to biological system running and more lessons should be drawn from nature. Given the large body of evidence discussed above, one can imagine that

adding noise to both controlled or assisted mechanical ventilatory modes represents the next gold standard for mechanical ventilation, which maybe not be far away!

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Too much, too little, too late: Treating status epilepticus without coma induction?*

The treatment of status epilepticus is a neurologic medical emergency requiring more coordination, timing, and delivery of treatment than almost any other

nonsurgical condition. Adding to this complexity is the growing list of anti-convulsants and sedative/anesthetics from which to choose for treatment. The last decade or so has brought new intravenous agents, such as valproic acid, levetiracetam, and lacosamide, which can be considered, but there is debate about when to use these. Can they be used before or in place of third-line barbiturates and benzodiazepines? What should the duration, dose, or order of these be? For instance, lacosamide looks very promising, but data are preliminary.

Levetiracetam may not work in acute treatment of status due to a 60-min delay in brain steady state concentration. Valproic acid works well for generalized tonic-clonic seizures, but adding it after phenytoin is slightly better, and combining the two in refractory status epilepticus (RSE) is slightly worse (1, 2). There is a dangerous lack of data about what treatment algorithms should look like, and success often depends more on the fortuitous choice than the informed.

Status is, to be sure, a very heterogeneous condition in which someone

*See also p. 2677.

Key Words: anticonvulsants; burst suppression; coma; electroencephalogram; status epilepticus

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presenting as a result of low anticonvulsant levels or alcohol toxicity has a much better chance of recovery than an elderly person with an acute neurologic insult, such as stroke, anoxia, or infection (3, 4). The later group is referred to as “potentially fatal” independent of status. There are as many types of status as there are seizures, such as tonic-clonic, complex partial, simple partial, myoclonic, continuous, and repetitive seizures; treatment may be different for each type and outcome relates in part to the seizure type. Nevertheless, recent adoption of across the board treatment for “impending status” using >5 mins of continuous seizures as the time to initiate aggressive treatment has probably helped outcome (5). The dilemma continues to surround what to do for up to 40% of patients who fail first- and second-line treatment and are therefore considered to have RSE (6), because meaningful recovery or survival is often poor for those whose seizures continue after 30 mins (7).

Harnessing GABAergic mechanisms to abort seizures early with adequate dosage of a benzodiazepine can be very effective. In fact, the receptor properties such as density and ionic environment might change as seizures continue, increasing resistance to treatment (8). First aid treatments such as buccal midazolam, rectal diazepam, and especially intramuscular midazolam may have the best chance of aborting the conversion to RSE (9). Thereafter, initiation of first-line therapy using intravenous lorazepam (preferred) or diazepam, followed by second-line antiepileptic drugs (AEDs) starting with phenytoin, and then a third-line agent such as propofol or midazolam is used. Published protocols for this reveal multiple variations and the resulting confusion can be deleterious due to delay in treatment orders. Dogmatic adherence to one or two algorithms may be very important for the individual practitioner, even if this looks substantially different from hospital-to-hospital. This is increasingly complicated by the limited supplies of routine anesthetics due to manufacturer backorder or delay.

Treatment failure or success may be most contingent upon how early in its course status is treated for many, but not all cases (10, 11). Studies in the early 90s seemed to indicate that when initial benzodiazepines fail, treatment should advance immediately to coma induction, because there has been evidence that second- and third-line additions rarely yield

more control (12). However, this would target one form or another of gamma aminobutyric acid (inhibitory) receptors, alone. A recent prospective study showed notable cessation of RSE with escalation of non-sedating AEDs. In fact, escalation with up to three non-sedating AEDs terminated RSE in >50% of patients (13). Indeed, second-line anticonvulsants (AEDs) are effective in some and can certainly avoid the range of complications and poor outcome for all patients after third-line therapy noted in this issue of *Critical Care Medicine* by Kowalski et al (14). Also important, the authors show that using pentobarbital as a third-line choice is especially risky. This leaves phenobarbital that profoundly depresses respiration and has a half-life of >48 hrs; midazolam requiring dose escalation due to tachyphylaxis; and propofol, which may cause metabolic acidosis, hypotension, and lipidemia termed *propofol infusion syndrome* (15). Other agents, such as thiopental, ketamine, or inhalation anesthetics, and interventions, such as vagal nerve stimulator, electroconvulsive therapy, hypothermia, or epilepsy surgery, have been used with variable success.

Status that has continued or recurred despite therapy with general anesthesia for ≥ 24 hrs is considered “Super-Refractory” (8). The ensuing cerebral damage includes structural changes in gross and histological anatomy. This is likely due to excitotoxicity driven by massive glutaminergic receptor overactivity causing a calcium influx cascade of necrosis or apoptosis (16). In this view, the primary aim is neuroprotection and, if seizures are ongoing, would require maximum suppression of all electrographic seizures with burst suppression on electroencephalogram. However, this is of questionable utility given the findings of Kowalski et al and the fact that there is no consensus as to whether burst suppression pattern is associated with better outcome in status. In addition, depth of suppression does not always predict response to the treatment (17).

Recommendations for successful treatment of RSE continue to demand strategies in the absence of data. Randomized controlled trials are difficult, but at least prospective observational study protocols should be developed. These might focus on the possibility of using two or more separate algorithms for treating status depending on the underlying cause and initial electrographic response to

benzodiazepine. For instance, a patient with periodic discharges from anoxia or stroke who has an electroencephalogram that responds to lorazepam could rarely benefit from rapid coma induction, whereas those with recurrent status from epilepsy or a partial change in consciousness would be better candidates for escalation of second-line AEDs. These should be large-scale, multicenter studies in which information is collected at the time of presentation. This may be the only reliable way to sort out efficacy of treatment choice as it relates to etiology and duration and type of status. Perhaps electronic data and increased emphasis on collaboration will finally make this possible.

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“What does not kill you makes you stronger”*

“What does not kill you makes you stronger.” This quote was previously used to describe investigation of preconditioning, where sublethal exposure to noxious stimuli resulted in a subsequent, more robust cellular response to stress. Ischemia is the best example of this phenomenon. The existence of multiple, diverse preconditioning stimuli that confer protection represents the familiar phenomenon of “cross-tolerance.” The purpose of this editorial is not to discuss the possibility of toxicity of inhalational anesthetic agents but to comment on the article “Sevoflurane preconditioning improves mitochondrial function and long-term neurological sequelae after transient cerebral ischemia: Role of mitochondrial permeability transition” by Ye et al (1) in this issue of *Critical Care Medicine*. This article adds some interesting and new information to the area of preischemic conditioning by volatile anesthetic agents. Such work has been presented in myocardial ischemia research, but the potential mechanism(s) of action and possibility of longer-term protection in brain have not previously been described.

Mitochondria are ubiquitous organelles responsible for many essential cellular processes in eukaryotic organisms and are considered the “gatekeepers of life and death.” The major functions of mitochondria include the production of >90% of ATP, the regulation of intracellular calcium, redox signaling, and the regulation of apoptosis. Given the important role of mitochondria

in neuronal physiology, it is not surprising that mitochondria actively participate in preconditioning signaling pathways.

What this study shows is the potential involvement of the mitochondria in neuroprotection provided by sevoflurane preconditioning (SPC) delivered for 60 mins at 24 hrs before transient cerebral ischemia in a rodent model. The authors showed that: 1) SPC reduced infarct volume at 14 days after reperfusion and improved neurological sequelae up to 6 wks after temporary focal cerebral ischemia; 2) SPC protected mitochondrial function evidenced by preserved respiratory chain complex activities, lowered mitochondrial hydrogen peroxide production, and hyperpolarized mitochondrial membrane potential during early reperfusion; 3) SPC significantly attenuated mitochondrial permeability transition pore (mPTP) opening in this model during early reperfusion, and isolated mitochondria demonstrated reduced sensitivity to Ca²⁺-induced mPTP opening after preexposure to sevoflurane *in vitro*; and 4) The beneficial effects of SPC could be negated by an mPTP opener and mimicked by an agent (cyclosporin A) that reduced mPTP opening.

The mPTP is an increase in the permeability of the mitochondrial membranes to molecules with molecular weight <1500 Da. mPTP results from the opening of a mitochondrial permeability transition pore, mPTP, that is formed in the inner membrane of the mitochondria under certain pathological conditions such as traumatic brain injury and stroke. Induction of the permeability transition pore can lead to mitochondrial swelling and cell death through apoptosis or necrosis depending on the particular biological setting and therefore is a plausible target for therapeutic intervention.

However, SPC has a limited effect on mitochondrial electron transfer chain II, and if the electron transfer chain process

is in “series” this presents a very serious limitation to SPC. The authors investigated the differential effects of SPC on electron transfer chain complex II activity and other complex (I, III, IV) activities. The authors reported that the data are stable (response to reviewer’s comments), having repeated this experiment several times with consistent results showing that SPC does not affect electron transfer chain complex II activity.

Complex II (succinate dehydrogenase) binds to the inner mitochondrial membrane. Despite minimal effects on complex II, SPC promoted complex I, III, and IV activities, and, importantly, preserved the general mitochondrial function (mitochondrial membrane potential) and reduced mitochondrial reactive oxygen species production. But why does SPC fail to affect complex II activity? The authors candidly responded to reviewers, “as translational scientists, frankly speaking, we currently have no answer. But we infer this may be related to the mPTP inhibition, because CsA also increases complex I, III, and IV activities, but not complex II (unpublished data).” Fascinatingly, it has been shown that ischemic preconditioning increases the activity of mitochondrial respiratory chain complexes I, III, and IV in synaptosomes isolated from rat hippocampus (2, 3).

More importantly, these changes are associated with improved longer-term histological and neurological outcome after cerebral ischemia. The importance of determining whether a neuroprotective strategy can improve long-term neurological outcome in animal studies is a key recommendation of the Stroke Therapy Academic Industry Roundtable. Stroke Therapy Academic Industry Roundtable strongly recommends that “Histological and behavioral studies need to include studies conducted at least 2 to 3 wks or longer after stroke onset to demonstrate a sustained benefit

*See also p. 2685.

Key Words: preconditioning; stroke; temporary cerebral ischemia

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