

under the assumption that the missing value was either the highest or the lowest recorded value.

By assigning the shortest intubation time (20 s), the median tracheal intubation time was 79 s using fiberoptic technique and 62 s with video laryngoscopic technique ($P = 0.33$). By assigning the longest intubation time (678 s), the median values are 80 and 72 s, respectively ($P = 0.75$). The success rate for tracheal intubation at first attempt was 80.4 and 69.4% for fiberoptic and video laryngoscopic techniques, respectively ($P = 0.22$), when the lowest number of attempts (1) was used. With the highest number of attempts (3) used for missing data, the corresponding rate at first attempt was 78.3 and 63.3% ($P = 0.11$). Therefore, these intention-to-treat analyses do not change the results substantially, and the conclusion is still the same.

Drs. Levine and Leibowitz are concerned that fiberoptic intubation is a threatened skill to learn and master. We do not advocate for abandoning fiberoptic intubation but merely examine an alternative intubation instrument that may be valuable for patients and anesthesiologists in difficult airway situations. Fiberoptic intubation is neither 100% safe for patients nor 100% reliable securing intubation in all patients with difficult airway. Therefore, alternatives are necessary, and we must constantly seek for the optimal intubation device that can be used for all patients with a safe and reliable result. Five patients in the McGrath VL group were excluded in accordance with our exclusion criteria to secure uniform airway analgesia for all included patients. However, to conclude that these patients could not undergo awake intubation is too excessive because awake intubation using other forms of topical anesthesia was not the topic of our study.

A mouth opening of at least 15 mm is necessary for introducing the McGrath video laryngoscope but is in fact less than that required for introducing the Macintosh and Miller laryngoscope. In addition, the video laryngoscopes improve the Cormack and Lehane grade one to two grades compared with the Macintosh and Miller laryngoscope. Therefore, we do not speculate that the Macintosh and Miller laryngoscope would have outperformed the McGrath video laryngoscope in our patient population. We did not want to inject directly into a tumor underneath the cricothyroid membrane, but to broaden this to state that we excluded all patients with neck pathology is an exaggeration. Patients, where transtracheal injection of local anesthetic failed, had at the time of inclusion been preanesthetically evaluated, and it was here judged possible to identify the cricothyroid membrane. In the future, ultrasound will possibly be helpful for correctly identifying the membrane in these patients where palpation fails.

Drs. Xue, Cheng, and Li state, "When adequate airway topical anesthesia is obtained, subsequent intubation is usually easy." In the future, we would welcome a randomized, sufficiently powered study of topical anesthesia using video laryngoscopes *versus* fiberscopes, including an extended assessment of the performance of airway topical anesthesia. Surely, different techniques for local anesthetizing the airway all have

advantages and disadvantages. The "spray as you go" technique may be unnerving to the less trained anesthesiologist because it causes coughing and perhaps a subsequent loss of vision when spraying through the fiberscope. Therefore, topical anesthesia may be achieved with the fiberscope but intubation may fail! We chose the transtracheal local anesthetic technique because of this procedure being the preferred method in the centers included in our study and because transtracheal anesthesia produces the least coughing during endoscopy.² However, mastering different topical anesthesia methods will most certainly prove helpful in handling patients with difficult airways.

Finally, we think that Drs. Xue, Cheng, and Li would agree with us in the theoretical concern that video laryngoscopes may cause more pressure on the pharyngeal/laryngeal structures than the fiberscope. In this context, manikin studies have limitations because of the anatomy of manikins not being directly transferrable to patients. Airway manikins upper airway "tissue are stiff, noncompliant and static rather than soft, fragile, and dynamic."³ For further elucidating this topic, we look forward to see the results of human studies.

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Controls Should Exist for Hyperoxic and Normoxic Conditions in All Experiments Involving Anesthetics

To the Editor:

Because anesthesia administration is a sure marker for supplemental oxygen use, the submolecular effects of any level of oxygen and the attendant oxidative stress that hyperoxia may cause should be accounted for in research. LeFrèche *et al.*¹ (and the accompanying editorial by Eckenhoff and Planel)² reference studies where tau phosphorylation was detected but the degree of oxygen used was not well documented.^{3,4} Even studies that rely on established models to parse anesthesia-induced neurotoxic/neuromodulatory

effects report oxygen levels of “approximately 24%” against controls exposed to 21% oxygen without addressing the fact that 24% oxygen is still a hyperoxic experimental condition, although much lower than 100%.⁵

Thus, even as Le Freche *et al.*¹ produce tantalizing data using a senescent mouse model of postoperative cognitive dysfunction and other tauopathies in aged patients, they also perpetuate a bigger problem. Although they report a 100% oxygen/null sevoflurane control for their 100% oxygen/sevoflurane (1.5% and 2.5%) short-term effects cohorts, they do not report a corresponding 100% oxygen/null sevoflurane control for the serial 100% oxygen/sevoflurane (1.5% and 2.5%) exposures in their long-term effects cohorts; nor do they report any form of 21% oxygen/sevoflurane control for any of their experiments, short- or long-term. In brief, they inadequately report on controls for the most powerful “drug” used in their studies: oxygen.

Why should this matter? Oxygen, reactive oxygen species, and associated free radicals are potent beneficial and detrimental subcellular event modulators.⁶ The stoichiometric nature of mitohormetic effects related to reactive oxygen species actions, membrane potential changes, peroxidation reactions, DNA damage, protein folding actions, and calcium homeostasis are increasingly recognized.^{7,8} Indeed, mitochondria can interact in networks to propagate the effects of small bursts of reactive oxygen species, thereby altering mitochondrial permeability transition pore function, among other effects.⁹ That this mitochondrial outer membrane complex may interact with the peripheral benzodiazepine receptor found in the same membrane presents an intriguing possible link between oxidative stress and anesthetic effects¹⁰—effects, which according to recent research cannot be ignored.¹¹

How does this relate to increased tau phosphorylation noted after the hyperoxic anesthesia used by LeFreche *et al.*?¹² Among the multiple mechanisms purported to cause tau hyperphosphorylation, oxidative stress is considered both a possible indirect and direct cause of tauopathy.¹² Specifically germane to LeFreche *et al.*'s study is the prior finding that oxidative stress without anesthesia can cause tau hyperphosphorylation.¹³ Because oxidative stress originates at the mitochondrial level, any factor that increases oxidative stress—such as hypoxia¹⁴ or hyperoxia¹⁵—may potentially influence tau hyperphosphorylation. Oxygen, then, would seem to require the tightest level of control wherever its effects might be anticipated.

Suppose serial 100% oxygen exposures or serial normoxic sevoflurane exposures actually produce tau phosphorylation levels equal to or higher than 100% oxygen/sevoflurane exposures. The controls used in LeFreche *et al.*'s¹ experiments do not sufficiently address this possibility. Given that “nonanesthesia induced” experimental tauopathy produced in an Alzheimer model is propagated over time from the entorhinal cortex toward the limbic system and associated cortices,¹⁶ the possibility that

iatrogenic “anesthesia-induced” tauopathy can spread similarly, irrespective of cause, becomes a legitimate concern in postanesthesia cognitive dysfunction modeling. In this regard, the possible role of hyperoxia, with or without anesthesia, in tauopathy induction—as well as other neurotoxicity/neuromodulatory models—deserves meticulous control in future investigations.

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In Reply:

Dr. Kopp raises an important point that Dr. Planel and I should have mentioned in our editorial.¹ There is no question that mitochondria, reactive oxygen species, and various neurodegeneration pathways, including tauopathy, are linked in some way. And there is also no question that we often treat patients (and animals and cells in our studies) with oxygen as if it is inert. It is most certainly not. However, there is a dearth of literature on the effect of inhaled oxygen on any of the neurodegenerative diseases, so it is not yet clear whether the hypothetical concern raised by Dr. Kopp is real and if so, of what magnitude? Until such data become available, it is important to take Dr. Kopp's advice and adequately control our studies with respect to oxygen.

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Other Factors to Consider When Deciding Whether or not to Infuse Volume Because of Arterial Blood Pressure Waveform Variation

To the Editor:

In their article, Biais *et al.*¹ list several limitations to the usefulness of the dynamic index of fluid responsiveness. I would suggest that one or two more (waning neuromuscular blockade and perhaps obesity) be considered as additions to the list.

First, the arterial pressure waveform variation (APWV, *i.e.*, pulse pressure variation, stroke volume variation,

systolic pressure variation, or delta down) studies generally have not considered the effect of a change in chest wall compliance. In most studies, the patients seemed to have been deeply paralyzed, and that is the condition from which recommendations seemed to have arisen. Anecdotally, I have been in situations where there has been significant APWV with decreased blood pressure and/or cardiac output, which improved dramatically just with neuromuscular blockade (NMB) administration. Presumably the treatment of truncal rigidity resulted in decreased intrathoracic pressure during positive pressure ventilation resulting in improved venous return and subsequent hemodynamic improvement and reduced APWV.

Second, all other things being equal, obese patients would be expected to require larger peak inspiratory pressures, which may result in a larger APWV as their baseline. Are the authors aware of any data that take obesity into consideration when considering the amount of APWV that indicates fluid therapy?

Treatment of APWV should not be the endpoint of therapy; it is a guide to therapy. The endpoint of therapy should be an adequate cardiac output (*i.e.*, adequate oxygen delivery) and blood pressure. Just because the hemodynamic situation will “improve” (by virtue of decreasing APWV) by administering fluid in a patient with APWV does not always mean that you should if the hemodynamics are already satisfactory. One runs the risk of giving excessive fluid to a patient who does not need additional fluid, particularly if the “mechanical” problem can be treated by other means (*i.e.*, NMB).

Although I agree that in typical anesthetic practice volume administration is likely to be what is indicated most often when one sees APWV, one should consider the state of paralysis and perhaps the use of NMB. This may result in an improved hemodynamic state without excessive fluid administration. Administering NMB may result in a lower volume infusion requirement and/or a better hemodynamic outcome than can be achieved by volume infusion only. Another potential benefit of NMB is that oxygen consumption may decrease, thereby allowing the patient to more easily meet his/her oxygen delivery needs, particularly if the cardiac output is marginal.

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