linearity requirements for Granger causality. For example, we found that 96% of EEG windows in the unmodified Granger analysis would have been excluded by the Durbin-Watson test for autocorrelation, but only 3.4% of EEG windows were excluded by the Durbin-Watson test if using the sign-reversed Granger method.

Another plausible explanation is that the sign-reversed Granger filtering of the narrowband oscillatory peaks in the spectra might, in some way, allow propofol-induced changes in underlying nonoscillatory broadband brain co-ordination to become more apparent. And that it is these processes that are mechanistically more important than the much more obvious oscillatory components in the altered information flow underlying loss of responsiveness. It is noteworthy that the process noise components of the Granger causality show the most dramatic decreases with unresponsiveness. Although a full theoretical understanding has not yet been developed, we suggest that researchers consider using sign reversal when applying Granger causality analysis to neurobiologic signals.

Research Support

Support was provided solely from institutional and/or departmental sources.

Competing Interests

The authors declare no competing interests.

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DOI: 10.1097/ALN.0000000000004511

This Research Letter is featured in "This Month in Anesthesiology," page A1.

Supplemental Digital Content

Supplementary Material, https://links.lww.com/ALN/D35

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(Accepted for publication January 12, 2023. Published online first on March 1, 2023.)

Flow Effects of High-flow Nasal Oxygenation: Comment

To the Editor:

While the ability of high-flow nasal cannula to achieve apneic oxygenation is well established, the ability to remove carbon dioxide is less clear. The recent investigation by Riva and colleagues on the issue, in which various flow rates were examined during apneic periods, interested us.[1] The study could not identify a meaningful ventilatory contribution attributable to high-flow nasal cannula. While we applaud the authors' methodology, we feel that the working methodology of high-flow nasal cannula needs to be considered in context with the conclusion and interpretation.

Variations in lung mechanics need to be considered when the interplay of high-flow nasal cannula oxygenation and carbon dioxide exchange are examined. Respiratory mechanics during high-flow nasal cannula oxygenation is likely to differ substantially between the paralyzed and unparalyzed states as in spontaneous and assisted or controlled breathing. The high-flow nasal cannula is believed to generate a level of pharyngeal pressure.[2] Thus, the air being expired from the lung will be opposed by the fresh gas flow from the high-flow nasal cannula, which will produce a positive end-expiratory pressure–like effect, changing the lung volume and influencing ventilation.[2,3] With paralysis, the resistance against the expiratory flow will be lost.

Furthermore, the continuous positive airway pressure–like effect of the high-flow nasal cannula with the patient's mouth open due to jaw thrust maneuvers, laryngoscopy, or the presence of an oropharyngeal airway in the paralyzed patient is difficult to envisage and probably negligible.[4] Nevertheless, these factors are likely to alter oropharyngeal gas washout, the mechanism whereby a high-flow nasal

cannula provides carbon dioxide removal.[5] Therefore, in our opinion, it will be premature to entirely dismiss the ventilatory effect of high-flow nasal cannula, especially in nonparalyzed patients.

We would welcome the authors' insights on these details. They should help readers incorporate the concept of flow-dependent ventilatory effects into their understanding of airway management in paralyzed patients.

Research Support

Support was provided solely from institutional and/or departmental sources.

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The corresponding author of the original article referenced above has read the letter and does not have anything to add in a published reply. —Evan D. Kharasch, M.D., Ph.D., Editor-in-Chief

DOI: 10.1097/ALN.0000000000004540

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(Accepted for publication February 9, 2023. Published online first on March 17, 2023.)

Diffusion Limitation of Volatile Anesthetic Uptake: Comment

To the Editor:

We read with great interest the study by Peyton[1] in which the effects of molar mass on the rate of diffusion of desflurane and nitrous oxide are compared. The author hypothesized the end-tidal-arterial partial pressure gradient for desflurane to be greater than nitrous oxide based on Graham's law of diffusion.[1] However, contrary to this hypothesis, the initial results showed a less than expected end-tidal-arterial partial pressure gradient for desflurane in comparison to nitrous oxide.[1] This finding was attributed to the higher rate of desflurane uptake.[1]

After adjusting for lung uptake rate of desflurane, the results showed no evidence of end-tidal-arterial gradient difference between the two gases.[1] Although this study should be prized for its sophisticated technical design, there are several reasons to be skeptical of its conclusion.

In order to achieve accurate results, we believe the study should be revised to account for the following. Our first observation relates to the patients included in the study. Table 1 in the article shows the reported oxygen uptake in this study is, note values in parentheses are SD, 166 (45) ml/min, and the reported carbon dioxide output is 166 (52) ml/min.[1] This shows a calculated respiratory quotient of 1. A respiratory quotient of 1 exceeds the normal of 0.8 and makes these patients ineligible for a study of this nature and furthermore renders the results unreliable. It should be noted that the data used for calculating dead space for an anesthetic gas (VDA/VAG)[1] in this study were taken from the previous study in which the reported respiratory quotient was claimed to be 0.8 and that in the subsequent study, the patient groups were described as similar.[2] The higher SD for carbon dioxide as compared to oxygen shows the possibility of a respiratory quotient of more than 1 in some patients.[1]

The authors allowed a range of concentrations from 2 to 3% for desflurane and from 10 to 15% for nitrous oxide in this study.[1] When the goal of the study is to compare