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.

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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

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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

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diffusion of two different gases, it would be prudent to choose a single concentration for both gases to eliminate the effect of concentration on partial pressure of inspired gas, end-tidal partial pressure of gas, and arterial partial pressure of gas.[1]

The author reported sample collections upon "achievement of near steady-state maintenance phase anesthesia between 30 to 60 min postinduction." While we can generally assume a clinically near steady state 30 min postinduction, if the goal is to compare the end-tidal-arterial gradient of these gases, then we should not assume a pharmacokinetically near steady state at 30 to 60 min as diffusion and redistribution of these gases follow two different rates during this period. Although during the first 10 to 15 min postinduction one can assume the same rate of diffusion and distribution due to almost identical blood/gas[3] and tissue/blood (brain/blood)[3] partition coefficients for these gases, the rate of muscle uptake for these gases is very different at the time of sampling. These gases have different muscle/blood partition coefficients: 2 for desflurane and 1.2 for nitrous oxide.[3] This results in a 1.67 times larger time constant for desflurane compared to nitrous oxide.[3] Considering 15% of cardiac output flows through muscle tissue with a mass equal to 43% of patient body weight, and muscle/blood partition coefficient of 1.2, one time constant for nitrous oxide for these patients (weight, 82.4 kg; cardiac output, 4 l/min)[1] will be 72 min and for desflurane will be 120 min.[3] This shows a larger rate of decline in uptake and distribution of nitrous oxide compared to desflurane at 30 to 60 min after induction.

Taking into consideration the ventilatory parameters in this study, choosing 6 l/min fresh gas flow would allow rebreathing.[1] Dilution due to rebreathing of expired gases will reduce the inspired partial pressures of both gases but has a greater effect on more diffusible gas compared to less diffusible gas,[3] making the achievement of steady state of inspired gas unreliable.

In conclusion, we should consider blood/gas solubility as the dominant factor for determining the gas exchange impairment[4] and recognize that the absence of blood solubility results in the absence of diffusion. The tissue/blood partition coefficient and timing of sampling should also be considered when comparing diffusibility of two gases if the gases have different tissue/blood partition coefficients.[1] Last, we should note the limitation of the measuring device used in the study. Datex-Ohmeda Capnomac Ultima (GE Healthcare, USA)[1] has an accuracy of 2 volume percent for nitrous oxide and 0.2 volume percent for desflurane. Considering the concentrations used for nitrous oxide and desflurane in this study, we can expect greater inaccuracy for nitrous oxide (20%) in comparison to desflurane (10%) and recognize that other properties, such as molar mass (the focus of this study) of a gas, may affect the rate of diffusion. This aspect warrants further investigation.

Competing Interests

The authors declare no competing interests.

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Diffusion Limitation of Volatile Anesthetic Uptake: Reply

In Reply:

I am grateful to Grigoryan *et al.*[1] for their interest in this study[2] and their comments. First, in an anesthetized, ventilated population, it is incorrect to simply assume that the respiratory quotient measured will be 0.8, the typical physiologic value determined by steady state metabolism in other situations. Patients are frequently in a state of mild to moderate hyperventilation, producing ongoing washout of the body's substantial carbon dioxide stores in addition to metabolic carbon dioxide production in the first hour or more after induction. This has been previously shown by us in this population, and average respiratory quotient values in excess of 0.9 are entirely expected.[3] Unlike our previous

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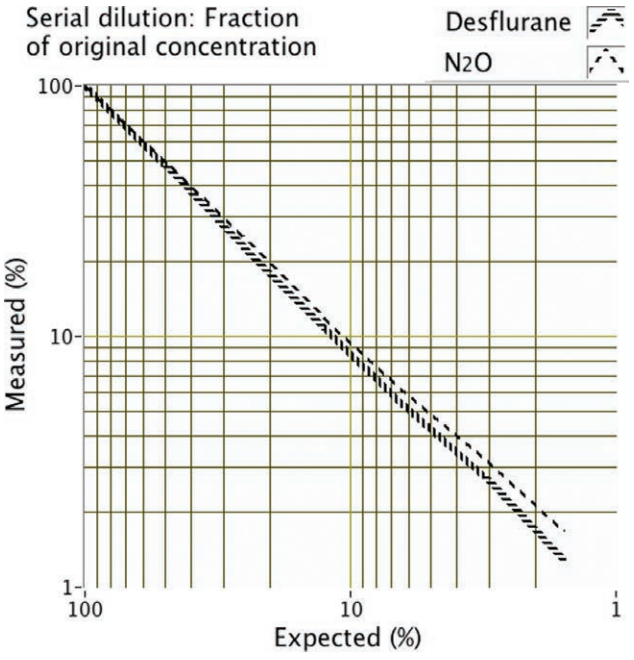
study comparing alveolar deadspace calculations for gases of different solubilities (where the findings would be little affected by the value assumed), a precise measurement of respiratory gas exchange was sought in the current study to achieve maximal precision in the comparison of the adjusted alveolar-arterial partial gradients for nitrous oxide and desflurane using equation 2.

This is one example of why "near steady state" most accurately describes the gas exchange state being studied during maintenance phase anesthesia. Grigoryan *et al.* point out correctly that the equations applied in the study assumed steady state inert gas uptake, which was done for simplicity. However, differentiation of standard equations predicting the typical exponential rate of change of anesthetic gas uptake[4] suggests that, after 30 min of anesthesia, less than a 2% relative error in estimation of alveolar-capillary gas uptake rate is expected from using steady state assumptions in the mass balance equations subsequently applied to the adjustment of alveolar-arterial partial pressure gradients for the two gases being compared. This would only make a trivial change to the study findings. Note that there was no significant difference for either gas between uptake measured in the gas and blood phases. The latter is not affected by lung "wash-in" corrections that are part of non–steady state lung gas uptake calculations. The differences in body kinetics between nitrous oxide and desflurane that Grigoryan *et al.* describe are indeed reflected in the different rates of lung uptake for the two gases clearly demonstrated in the study. The minimal rebreathing expected at the fresh gas flow rate used is accounted for, as calculation of uptake rate measured in the breathing system included the difference between inspired and expired flows (equation A6).

The reasons for the choices of inspired concentration of each gas are mentioned in the Materials and Methods. There were no advantages in delivering identical concentrations instead for the two gases, which are measured by infrared gas analyzers calibrated to operate over different clinically relevant concentration ranges. In fact, the best way to deal with the "concentration effect" that the authors allude to was to choose different concentrations that achieved a similar "effective" blood gas partition coefficient (*i.e.*, adjusted for inspired concentration; see reference 14) that corrected for the expected modest difference in the partition coefficient between nitrous oxide and desflurane (listed in table 2).

The authors' concerns about the limits of precision of the measurement device used are dealt with in reference 13. The accuracy of the Datex Capnomac (GE Healthcare, USA) in static gas partial pressure measurement for desflurane has been characterized using precise volumetric standards and found to be within 1% (relative) of predicted, and the resulting accuracy and precision of headspace equilibration measurement of partial pressures in blood were also assessed and were shown to be similar to those achieved by previous workers using gas chromatography. Similar relative accuracy and precision were found for nitrous oxide measurement. However, the foremost prerequisite for measurement of the partial pressure cascade, including alveolar-arterial gradient, for any inert gas is a high degree of linearity of the analyzer over the relevant range. The figure shows this for measurement by the device of a nitrous oxide–desflurane mixture in a gas-tight glass syringe during serial dilution in nitrogen over a 64-fold concentration range that spans the partial pressures encountered in the study. R^2 was greater than 0.999 for both gases.

The advantages of using a tidal gas monitor like the Capnomac, interfaced with a computer for real-time waveform capture, are substantial when studying alveolar-arterial gradients, as it obviates the practical difficulties in obtaining a reproducible end-expired gas sample uncontaminated by deadspace gas for subsequent gas analysis (by a gas chromatography, for instance). Last, I would take this opportunity to urge all investigators in this field to develop and validate simple assays for blood partial pressure measurement of inhalational agents if intending to study their pharmacology, as the presence of typical alveolar-arterial partial pressure gradients for inhalational anesthetics makes the commonly practiced reliance on end-tidal gas concentration measurements inadequate to accurately characterize their pharmacokinetics for many purposes.



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Competing Interests

Dr. Peyton has received research consultancy payments from Maquet Critical Care/Getinge (Stockholm, Sweden) for an unrelated project.

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Aortic Biomechanics: Comment

To the Editor:

We read with interest the recent review of aortic biomechanics and their clinical applications by Gregory *et al.*[1] The authors should be congratulated for addressing this important but often underappreciated subject. Nevertheless, we are obligated to mention that the authors did not acknowledge or discuss a series of pertinent studies conducted in chronically instrumented dogs describing the effects of anesthetics on aortic biomechanics. This canine model is highly relevant to the review,[1] because the cardiovascular effects of anesthetics are virtually identical in dogs and humans. We and others used aortic input impedance spectra in the frequency domain[2] that were interpreted with a three-element Windkessel model of the arterial circulation, incorporating aortic mechanical properties,[3] to quantify the effects of anesthetics on left ventricular afterload.[4–13] We first demonstrated that isoflurane reduces total arterial resistance in a concentration-dependent manner and modestly increases total arterial compliance (primarily determined by the aorta and proximal great vessels[14]), but does not affect characteristic aortic impedance (the resistance of the aorta itself).[4] In contrast, the potent vasodilator sodium nitroprusside decreased total arterial resistance and markedly increased total arterial compliance when the drug was administered at infusion rates that resulted in levels of hypotension equivalent to those observed during the administration of isoflurane. The findings with sodium nitroprusside confirmed previous observations in dogs[15] and humans.[16,17] Taken together, these data indicated that the primary effect of isoflurane on the determinants of left ventricular afterload was related to its well-known actions on arteriolar resistance vessels and not on the aorta itself, whereas sodium nitroprusside altered left ventricular afterload through its effects on both arteriolar vasomotor tone and the mechanical properties of the aorta. Similar findings with isoflurane were also reported in an acutely instrumented open-chest swine model.[13] We further showed that desflurane also reduces total arterial resistance but does not substantially affect total arterial compliance and characteristic aortic impedance, actions that were indistinguishable from those of isoflurane.[6] However, sevoflurane did not affect total arterial resistance but caused small increases in total arterial compliance and characteristic aortic impedance,[6] observations that mirrored those seen with the obsolete volatile anesthetic halothane.[4]

Isoflurane increased aortic distensibility (concomitant with reductions in aortic pressure) and did not affect characteristic aortic impedance when these parameters were calculated using simultaneous measurements of aortic diameter, pressure, and blood flow.[5] These findings reinforced the conclusion that alterations in the aortic mechanical properties are not responsible for the actions of isoflurane on left ventricular afterload. In contrast to the findings with isoflurane in dogs with normal left ventricular function, this volatile anesthetic did not exert beneficial changes in total arterial resistance, characteristic aortic impedance, and total arterial compliance in a canine model of heart failure with reduced ejection fraction induced by chronic rapid ventricular pacing.[7] We conducted additional investigations in normal and cardiomyopathic dogs with the anesthetic noble gas xenon,[8] and with the intravenous anesthetics propofol,[9,10] etomidate,[11] and dexmedetomidine[12] that revealed unique insights into the actions of these medications on the contributions of altered aortic mechanics to left ventricular afterload *in vivo*. These studies document that the impact of anesthetics on aortic biomechanics has been examined previously in clinically relevant animal models, contrary to the article's assertion.[1]

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