Middle ear pressure change during controlled breathing with gas mixtures containing nitrous oxide

WILLIAM J. DOYLE AND JULIANE M. BANKS

Department of Pediatric Otolaryngology, Children's Hospital of Pittsburgh and the Department of Otolaryngology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213

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Doyle, William J., and Juliane M. Banks. Middle ear pressure change during controlled breathing with gas mixtures containing nitrous oxide. J Appl Physiol 94: 199–204, 2003; 10.1152/japplphysiol.00634.2002.—The change in middle ear pressure while breathing gas mixtures containing N2O was studied in four monkeys. At each of three experimental sessions, monkeys were anesthetized, acclimated for 60 min, breathed with room air for 60 min, and then breathed with 5, 10, or 20% N2O for 60 min. Middle ear pressure, rectal temperature, and vital signs were recorded throughout. The time constant for blood-middle ear N2O exchange was calculated from these data. Middle ear pressure decreased during acclimation, was stable during air breathing, and increased during N2O breathing. The rate of pressure change was similar for both ears of each animal and was directly related to N2O percent. The calculated time constant ranged from 0.003 to 0.008 min⁻¹ across animals but was not different for a given ear across sessions. These results show that breathing gas mixtures containing N2O causes predictable and quantifiable increases in middle ear pressure.

time constant; animal model; gas exchange

THE EFFICIENCY OF THE MIDDLE EAR system as an energy coupler between air and liquid is inversely related to the absolute value of the pressure difference between the middle ear airspace (ME) and the ambient environment (5). Because the ME is a relatively fixed-volume, temperature-stable biological gas pocket, its pressure depends on the number of contained moles of gas. By extension, when isolated from communication with the external environment (e.g., time between successive Eustachian tube openings), the rate of change in total ME pressure depends on the rates of transmucosal (ME-blood) exchange of the physiological gases (H2O, N2, O2, and CO2) and on the rates of production (CO2) and consumption (O2) of the reactive gases. The transmucosal gas exchange rate is determined by factors that are independent of the particular gas species such as ME surface area, mucosal thickness, and volume blood flow and by gas-specific factors such as the extant partial-pressure gradient and species solubility in the mucosa and/or blood (5).

For both normal and diseased MEs, the measured ME-blood O2 and CO2 pressure gradients are approximately equal to zero, whereas that for N2 approximates 50 Torr (10, 12, 13). Therefore, total pressure of the isolated ME will decrease as N2 diffuses from ME to blood, a process that will continue until N2 pressure equilibrium is established. This loss of N2 from the ME drives the ME-ambient total pressure gradient to disequilibrium, thereby compromising the efficiency of the transducer function of the middle ear system. Periodic opening of the Eustachian tube allows for bolus gas exchange between nasopharynx (near ambient pressure) and ME, which decreases the ME-ambient pressure gradient. Thus the transducer function of the middle ear system is constrained by the efficiency of ME pressure regulation, which, ideally, maintains a dynamic equilibrium between volume gas loss due to transmucosal N2 exchange and volume gas influx during Eustachian tube openings (5).

Whereas many previous studies described the contribution of Eustachian tube function to ME pressure regulation (1, 2, 18), relatively few measured the rate of pressure decrease due to transmucosal exchange of the physiological gases; i.e., the demand placed on the Eustachian tube for gas resupply (6–8). Regarding the latter, it was shown that the exchange rates of reactive gases (O2 ad CO2) are very fast (relatively large time constants vis à vis inert gases) and primarily diffusion limited, whereas the exchange of the inert gas N2 is very slow and primarily perfusion limited. Because the N2 exchange rate is the main determinant of the rate of total ME pressure change, an accurate estimate of that rate is fundamental to understanding ME pressure regulation.

At physiological partial-pressure gradients, the rate of transmucosal N2 exchange is not easily measured because of its extremely slow rate of exchange (6, 7). To overcome this difficulty, the more soluble, perfusion-limited gas N2O has been used to study transmucosal inert gas exchange (7–9, 11, 15, 19, 20). On the basis of solubility considerations, the transmucosal exchange of N2O is estimated to be 30–40 times faster than that of N2 at identical driving pressures, thus allowing for

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Address for reprint requests and other correspondence: W. J. Doyle, Dept. of Pediatric Otolaryngology, Children’s Hospital of Pittsburgh, 3705 Fifth Ave., Pittsburgh, PA 15213 (E-mail: docdoyle2@aol.com).

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experimental measurement of its exchange rate over a reasonable time period.

Previously, an increase in ME pressure was reported for anesthetized patients breathing gas mixtures that included N₂O (3, 4, 11, 14–16), and, more recently, that response was used to compare transmucosal inert gas-exchange rates between ears with and without pneumatized mastoid regions and between ears with and without concurrent disease (9, 17, 19, 20). Although this approach provides a promising method to study the effects of altered ME conditions on transmucosal inert gas exchange, the majority of data for blood to ME N₂O exchange were acquired in the surgical setting where control over certain confounding variables such as gas mixture, blood-gas partial pressures, body temperature, and forced tubal openings was not maintained. Also, data presentation was limited to comparative descriptions of pressure-time functions, and no formal method was developed to quantitate the results in terms of a transmucosal time constant. In this paper, blood-to-ME exchange of N₂O was studied in cynomolgus monkeys under well-controlled experimental conditions. A mathematical description of the exchange process and formal methods to estimate the time constant for transmucosal N₂O exchange are presented.

MATERIALS AND METHODS

**Protocol.** Four juvenile cynomolgus monkeys weighing between 2.1 and 3.2 kg were used in the experiments. For each of three experimental sessions done on different days, the monkey was sedated with 30 mg of ketamine and anesthetized with “monkey mix” (10 mg/kg ketamine, 2 mg/kg xylazine; 0.3 mg/kg acepromazine). The monkey was monitored for ME pressure by tympanometry, for temperature by rectal probe, and for vital signs over a 60-min period (10-min intervals for ME pressure by tympanometry, for temperature by rectal probe, and for vital signs over a 60-min period (10-min intervals) to allow for physiological acclimation to the anesthetized state. Then the monkey was intubated, and the endotracheal tube was placed on-line to the output of a probe, and for vital signs over a 60-min period (10-min for ME pressure by tympanometry, for temperature by rectal probe, and for vital signs over a 60-min period (10-min intervals for ME pressure by tympanometry, for temperature by rectal probe, and for vital signs over a 60-min period (10-min intervals). The monkey was monitored during the experiment and for vital signs after the experiment. At the termination of the experiment, the animal was breathed for 200 MIDDLE EAR N₂O EXCHANGE

Below we present a mathematical description that defines these conditions and the methods for calculating the time constant for transmucosal N₂O exchange.

The pressure of any closed, gas filled compartment such as the ME (m) is described by the general gas law, or

\[
P_m^V = N_m^V R T_m
\]

where \(P_m^V\) is pressure, \(V_m^V\) is volume, \(N_m^V\) is number of moles of gas, \(T_m\) is the temperature of the ME, and \(R\) is the general gas constant. Total ME pressure is equal to the sum of the partial pressures of the physiological gases and any represented, nonphysiological species (e.g., N₂O). The change in total ME pressure is equal to the sum of the changes in the partial pressures of those gases, or

\[
\delta P_m^V / \delta t = (\delta P_{N_2}^m + \delta P_{CO_2}^m + \delta P_{N_2O}^m + \delta P_{O_2}^m + \delta P_{CO}^m) / \delta t
\]

where \(P_m^V\) is the partial pressure of a test gas. Under physiological conditions and at constant blood partial pressures for \(O_2\) and \(CO_2\), the ME-blood partial-pressure gradient for \(O_2\) and \(CO_2\) is \(\sim 0\) Torr and the ME is saturated with water vapor (10, 12, 13). Because there is no gradient to drive the ME-blood exchange of these gases, \(\delta P_{O_2}^m / \delta t = \delta P_{CO_2}^m / \delta t = 0\) Torr/min. Thus, for the ME of an acclimated, anesthetized animal breathing gas mixtures containing N₂O, Eq. 2 reduces to

\[
\delta P_m^V / \delta t = (\delta P_{N_2}^m + \delta P_{N_2O}^m) / \delta t
\]

Direct measurements in monkeys show that the change in ME \(N_2\) pressure at extant ME-blood gradients as high as 50 Torr is not measurable in experiments lasting for 4 h (6–8). Therefore, in relatively short-duration experiments, the effective \(N_2\) exchange rate is 0 Torr/min, and Eq. 3 becomes

\[
\delta P_m^V / \delta t = \delta P_{N_2O}^m / \delta t
\]

In the experiments described here, the N₂O pressure in the arterial blood is increased during controlled breathing with the gas mixtures. There, the change in the number of moles of N₂O in the ME compartment must be equal to the extant difference between the number of moles of that gas in the local arterial (a) and venous (v) blood compartments, or

\[
\delta N_{N_2O}^m = (N_{N_2O}^a - N_{N_2O}^v)
\]

For blood (b), the number of moles of a gas is directly related to the partial pressure (\(P_m^b\)) and solubility (\(S_m^g\)) of the gas in blood and the extant, local blood volume (\(V_m^b\)), or for N₂O

\[
N_{N_2O}^b = V_m^b P_m^b S_{N_2O}^m
\]

Recognizing that N₂O solubility is the same for arterial and venous blood (\(S_{N_2O}^a = S_{N_2O}^v\)), substituting the expressions for pressure from Eq. 1 and 6 for moles of gas in Eq. 5 and rearranging terms yields

\[
\delta P_{N_2O}^m / \delta t = (R T_m) / (V_m^b) (P_m^b V_m^b - P_{N_2O}^m V_m^b)^{-1}
\]

Dividing both sides of this equation by a time interval (\(\delta t\)) and noting that by continuity \(V_m^b / \delta t = V_m^b / \delta t = ME\) blood flow (\(Q_m^V\)), yields

\[
\delta P_{N_2O}^m / \delta t = (R T_m Q_m^V) (P_m^b V_m^b - P_{N_2O}^m V_m^b)^{-1}
\]

Under the experimental conditions, the ME pressure of N₂O must at all times be less than or equal to that of the local arterial and venous blood such that

\[
P_{N_2O}^m \leq P_{N_2}^m \text{ and } P_{N_2O}^m \leq P_{N_2}^v
\]

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or

$$-P_{N_2O}^m \approx -P_{N_2O}^v$$  \hspace{1cm} (9b)$$

Adding $P_{N_2O}^m$ to both sides of Eq. 9b yields

$$P_{N_2O}^m - P_{N_2O}^v \approx P_{N_2O}^m - P_{N_2O}^v$$  \hspace{1cm} (10a)$$

or

$$F_{N_2O}(P_{N_2O}^m - P_{N_2O}^v) = P_{N_2O}^m - P_{N_2O}^v$$  \hspace{1cm} (10b)$$

where $1 \geq F_{N_2O} \geq 0$. Substituting the result from Eq. 10b into Eq. 8 and combining with Eq. 4 yields

$$\delta P_{N_2O}/\delta t = \delta P_{N_2O}^m/\delta t = (F_{N_2O} R Q m T m S_{N_2O}^b) (P_{N_2O}^m - P_{N_2O}^v) (V_m)^{-1}$$  \hspace{1cm} (11)$$

This equation relates the rate of change in ME pressure ($\delta P_{N_2O}^m/\delta t$, determinable from experimental data) to the product of the extant arterial-ME $N_2O$ pressure gradient ($P_{N_2O}^m - P_{N_2O}^v$, determinable from experimental data); the general gas constant ($R$); the inverse of ME volume ($V_m^{-1}$), a constant; ME temperature ($T_m$, measured to be constant); $N_2O$ solubility in blood ($S_{N_2O}^b$, a constant); local volume blood flow ($Q_m$), and the ratio of arterial-venous $N_2O$ gradient to arterial-ME $N_2O$ gradient ($F_{N_2O}$). If $Q_m$ and $F_{N_2O}$ are constants for each experiment, Eq. 11 is linear and the rate of change in ME pressure divided by the extant arterial-ME $N_2O$ pressure gradient is a time constant, such that

$$(\delta P_{N_2O}^m/\delta t) (P_{N_2O}^m - P_{N_2O}^v) = F_{N_2O} R Q m T m S_{N_2O}^b (V_m)^{-1} = K_{N_2O}^m$$  \hspace{1cm} (12)$$

Note that violation of these assumptions (i.e., within-session changes in $Q_m$ or $F_{N_2O}$) will be reflected as a nonlinear relationship between the rate of ME pressure change ($\delta P_{N_2O}^m/\delta t$) and gradient ($P_{N_2O}^m - P_{N_2O}^v$), and consequently linearity between those variables is a testable hypothesis of assumption validity.

**Data structure.** The primary data for each experiment consist of the repeated measurements of bilateral ME pressure during the period of controlled breathing with the gas mixture. To calculate a time constant for transmucosal $N_2O$ exchange by Eq. 12, these data were transformed into estimates of the extant arterial-ME $N_2O$ pressure gradient and of the instantaneous rate of change in ME pressure.

For the period of controlled breathing with the $N_2O$ gas mixture, arterial $N_2O$ pressure ($P_{N_2O}^m$) is assumed to be constant and was estimated by multiplying the physiological blood $N_2O$ pressure (~570 Torr at 760 Torr ambient pressure) by the fraction of $N_2O$ in the breathing mixture (i.e., % substitution of $N_2O$ for $N_2$). At the onset of breathing the gas mixture ($t = 0$ min), ME $N_2O$ pressure ($P_{N_2O}^m$) is 0 Torr and, by Eq. 4, that partial pressure at any time can be estimated as the difference between ME pressure at that time ($t = i$) and ME pressure at $t = 0$. These estimates were used to calculate the extant ME-blood $N_2O$ pressure gradient [$G_{N_2O}^{t=i}$] as given by

$$G_{N_2O}^{t=i} = P_{N_2O}^m - (P_{N_2O}^{t=i-1} - P_{N_2O}^{t=i-0})$$  \hspace{1cm} (13)$$

The instantaneous rate of change in ME pressure was not measured in the experiment. However, that rate can be estimated by the slope of the linear portion of the function relating ME pressure to time. Here, we calculated the slope of that function for the 60 min of controlled breathing with the $N_2O$ gas mixture by using least-squares linear regression. That procedure also provides an estimate of the goodness of a linear fit to the data distribution that is given by the percent variance in ME pressure explained by the regression on time ($r^2 \times 100\%$). For all experimental sessions, that estimate was >89%, and consequently we accepted the regression slope as a reasonable estimate of the instantaneous rate of change in ME pressure, $\delta P_{N_2O}^m/\delta t$.

From Eq. 12, the time constant for $N_2O$ exchange was calculated as the ratio of the instantaneous rate of change in ME pressure to the average (over the period of breathing the $N_2O$ gas mixture) value of the estimated ME-blood $N_2O$ pressure gradient, or

$$K_{N_2O}^m = (\delta P_{N_2O}^m/\delta t) / G_{N_2O}^{avg}$$  \hspace{1cm} (14)$$

Fig. 1. Left (●) and right (○) middle ear (ME) pressure as a function of time for monkey 2 at experimental sessions 1 (A; 5% $N_2O$), 2 (B; 10% $N_2O$), and 3 (C; 20% $N_2O$). For each session, the data for the first 60 min correspond to an acclimation period, for the second 60 min to respirator-controlled breathing with room air, and for the third 60 min to respirator-controlled breathing with the $N_2O$ gas mixture.
The two ears of each monkey. For each ear, that rate of ME pressure change at each session was similar for the linear model (explained variance $r^2$) calculated by linear regression equation relating middle ear pressure to $N_2O$ exposure time for all experiments.

### Table 1. Linear regression equation relating middle ear pressure to $N_2O$ exposure time for all experiments

<table>
<thead>
<tr>
<th>Monkey</th>
<th>Ear</th>
<th>Session 1</th>
<th>Session 2</th>
<th>Session 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Right</td>
<td>1.30 ± 0.08 (0.96)</td>
<td>3.55 ± 0.09 (0.99)</td>
<td>5.17 ± 0.21 (0.98)</td>
</tr>
<tr>
<td>1</td>
<td>Left</td>
<td>1.19 ± 0.07 (0.97)</td>
<td>3.29 ± 0.20 (0.97)</td>
<td>4.88 ± 0.28 (0.97)</td>
</tr>
<tr>
<td>2</td>
<td>Right</td>
<td>1.28 ± 0.14 (0.89)</td>
<td>3.54 ± 0.12 (0.99)</td>
<td>6.57 ± 0.11 (1.00)</td>
</tr>
<tr>
<td>2</td>
<td>Left</td>
<td>1.65 ± 0.19 (0.89)</td>
<td>3.61 ± 0.16 (0.98)</td>
<td>7.02 ± 0.15 (1.00)</td>
</tr>
<tr>
<td>3</td>
<td>Right</td>
<td>1.41 ± 0.05 (0.99)</td>
<td>2.40 ± 0.08 (0.99)</td>
<td>3.89 ± 0.03 (0.99)</td>
</tr>
<tr>
<td>3</td>
<td>Left</td>
<td>1.09 ± 0.07 (0.96)</td>
<td>2.61 ± 0.08 (0.99)</td>
<td>3.71 ± 0.21 (0.97)</td>
</tr>
<tr>
<td>4</td>
<td>Right</td>
<td>2.41 ± 0.12 (0.98)</td>
<td>3.56 ± 0.18 (0.97)</td>
<td>8.43 ± 0.56 (0.96)</td>
</tr>
<tr>
<td>4</td>
<td>Left</td>
<td>2.63 ± 0.16 (0.96)</td>
<td>3.94 ± 0.27 (0.95)</td>
<td>9.35 ± 0.54 (0.97)</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td>1.62 ± 0.20</td>
<td>3.31 ± 0.18</td>
<td>6.13 ± 0.73</td>
</tr>
</tbody>
</table>

Values are slope ± SE (in mmH$_2$O); values in parentheses are square of the Pearson product moment correlation coefficient ($r^2$) for middle ear (ME) pressure vs. time.

The calculated time constant was examined for consistency across ears and animals and for independence of gas mixture (i.e., session). Vital signs and temperature measurements served to document stable values during the data collection period of each experimental session.

### RESULTS

Figure 1 shows the left and right ME pressure-time functions of one monkey (monkey 2) for the experimental sessions that included a 60-min period of controlled breathing with a gas mixture containing 5 (C), 10 (B), and 20% (C) $N_2O$. For all three sessions, the 60-min acclimation period (minutes 0–60) was characterized by a variable magnitude decrease in ME pressure. This decrease was temporally related to a concomitant decrease in body temperature (data not shown). During the second 60-min period (minutes 60–120) wherein the animal was breathed by respirator with room air, bilateral ME pressures were relatively stable, indicating no measurable gas transfers to or from the ME. In contrast, the third 60-min period corresponding to controlled breathing with the experimental gas mixture (minutes 120–180) was characterized by a near-constant rate of ME pressure increase. The rate of change in ME pressure was similar for both ears at each session, and that rate was greater at higher percent $N_2O$ compositions in the breathing mixture. This temporal pattern of ME pressure change characterized the experiments on the other three monkeys, although the pressure-time function of monkey 4 for controlled breathing with gas mixtures containing 20% $N_2O$ showed bilateral evidence of passive Eustachian tube opening (an abrupt decrease in ME pressure).

The slope of the ME pressure-time function for the 60 min (45 min for monkey 4 at session 3) of controlled breathing with the experimental gas mixture estimates the instantaneous rate of change in ME pressure effected by transmucosal $N_2O$ exchange. That slope calculated by linear regression equation for all experiments in Table 1. Also listed for each experiment is the square of the Pearson product moment correlation coefficient ($r^2$) for the pressure vs. time data. The large $r^2$ value for all experiments documents an excellent goodness of fit for the linear model (explained variance $\geq 89\%$). The rate of ME pressure change at each session was similar for the two ears of each monkey. For each ear, that rate increased in direct proportion to the percent $N_2O$ composition of the breathing mixture with approximate rate ratios of 4:2:1 for experiments conducted using gas mixtures containing 20, 10, and 5% $N_2O$, respectively.

Figure 2 shows a scatterplot of the rate of change in ME pressure vs. the arterial-ME $N_2O$ pressure gradient for the eight ears at the three study sessions. At any session, there was a large variability in the rate of pressure change for the eight ears, but those rates were more similar for the left and right ears of each monkey compared with the rates for different monkeys. Also, for individual ears there was an apparent linear relationship between the rate of ME pressure change and the respective arterial-ME $N_2O$ pressure gradient. The time constant for transmucosal $N_2O$ exchange was estimated as the ratio of the rate of ME pressure change to the respective $N_2O$ pressure gradient (See Eq. 14). Table 2 lists the time constant calculated for each experiment. The value of the time constant ranged from 0.003 to 0.008 min$^{-1}$, was similar for the two ears of each monkey, and was not influenced by the percent $N_2O$ in the breathing mixture.

### DISCUSSION

In these experiments, ME pressure showed a decrease attributable to decreasing body temperature increases directly with increasing $N_2O$ gradient. The time constant for transmucosal $N_2O$ exchange equals the ratio of the rate of ME pressure change to the corresponding arterial-ME $N_2O$ gradient.
over the first hour after administration of the anesthetic. For the 1-h period of air breathing, ME pressure was relatively stable for all ears at all study sessions. This documents no measurable gas transfers to or from the ME during that period (Eq. 2), a requirement of the method used to estimate the N2O time constant. Like the results of clinical studies reported previously (3, 4, 11, 14–16), breathing gas mixtures containing N2O caused significant increases in the tympanometrically measured ME pressure of all four monkeys. Moreover, for the 60 min of controlled breathing with each experimental gas mixture, the relationship between ME pressure and exposure time was linear. From Eq. 11, this observation requires that the effects of gas exchange on the arterial-ME N2O pressure gradient be negligible for that interval (i.e., $P_{N2O}$ measured at $t = 0 \sim P_{N2O}^M$ and $P_{N2O}$ measured at $t = 60$) and that the ME volume, blood flow, and the gradient ratio ($F_{N2O}$) be constant over that interval. In support of the former, calculation of the percent change in gradient $[G' = 60\%N2O - G' = 0\%N2O]/G' = 0\%N2O \times 100\%$) yielded average values of 9 ± 3, 12 ± 1, and 10 ± 2% for sessions 1, 2, and 3, respectively. Thus the requirements of the mathematical description underlying estimation of the time constant appear to be satisfied by the conditions of the experiment. The measured value of the time constant for transmucosal N2O exchange in juvenile cynomolgus monkeys is on the order of $10^{-4}$ min$^{-1}$.

The linear relationship between the rate of ME pressure change and the calculated arterial-ME N2O gradient for each ear shows that the time constant is independent of the N2O percent composition in the breathing mixture. This implies that the above listed parameters are relatively constant over the extended period of time between sessions and that the mucosal blood flow ($Q_m$) and the gradient ratio ($F_{N2O}$) are independent of the arterial N2O pressure. These results show that measurement of the time constant for transmucosal N2O exchange using the methods described in this report is reproducible over time. Moreover, in experiments designed to evaluate the effects of specific ME conditions on transmucosal inert gas exchange, a specific driving partial pressure for the exchange (e.g., N2O percent composition of breathing mixture) is not required but can be chosen on the basis of the requirements of each experiment.

A practical application of measuring the time constant for transmucosal N2O exchange is to estimate that constant for N2, a physiological gas whose transmucosal exchange is rate limiting to the development of ME under pressure. However, the gradient ratio ($F_{N2O}$) included as a parameter in Eq. 12 may limit the use of the time constant measured for one gas species to estimate that for a second. Specifically, inert gas exchange constants are usually assumed to be scaled as the ratio of their respective solubilities in the exchange medium, i.e., $K_{g1} = K_{g2}(S_{g1}/S_{g2})$ where $K_{g1}$ and $K_{g2}$ and $S_{g1}$ and $S_{g2}$ are the transmucosal time constants ($K_{g}$ measured, $K_{g}$ estimated) and known solubilities, respectively, for two inert gas species. However, the ratio of time constants defined by Eq. 12 for any two gases is $F_{g1}S_{g1}/F_{g2}S_{g2}$, which reduces to a ratio of gas solubilities if and only if $F_{g1} = F_{g2}$. The validity of identical gradient ratios for different inert gas species is not known and must be evaluated empirically by experiment. Lacking proof of that identity, the measured time constant for transmucosal N2O exchange cannot be used with certainty to estimate the time constant for transmucosal exchange of other inert gases such as N2. However, conditional relationships defined for the N2O time constant will characterize the N2 time constant. For example, if the measured value of the N2O time constant is X times greater under condition 1 compared with condition 2, the expected ratio of the N2 time constants for those conditions will also be X. Specifically, if $K_{N2O} = XK_{N2O}'$, then by substitution: $K_{N2O}' = (F_{N2O}S_{N2O}F_{N2O}S_{N2O})/XK_{N2O}'$, where the prime ($'$) designates a different condition.

The method to estimate the time constant for transmucosal inert gas exchange described in this report is applicable to situations in which the exchange can be modeled as a primarily perfusion limited transfer of gas across a biological barrier. For example, it can be used to describe quantitatively the effects of abnormal ME conditions such as mucosal inflammation or arrested mastoid air-cell development on transmucosal inert gas exchange. However, other pathological conditions such as the presence of a ME effusion introduce additional exchange compartments (ME fluid) into the system and require significant modification of these methods for accurate estimation of a time constant.

Previous studies reported increases in ME pressure for anesthetized humans breathing complex gas mixtures that included N2O (3, 4, 11, 14–16). Whereas pressure-time functions can be abstracted from those data, transformation to estimates of the time constant for transmucosal N2O exchange is valid only if the measured ME pressure change is wholly attributable to transfer of that gas from blood to ME. This requires that, for the period of data collection, no other gases are in disequilibrium between blood and ME (with the exception of gases that diffuse too slowly to affect pressure), body temperature remains constant, the anesthetic does not change ME blood flow, and the Eustachian tube does not vent gas. Because the gas mixture is administered to induce anesthesia and pressure.

### Table 2. Calculated time-constant for transmucosal N2O exchange for each experiment

<table>
<thead>
<tr>
<th>Monkey</th>
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<th>Session 1</th>
<th>Session 2</th>
<th>Session 3</th>
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</tbody>
</table>

Values are given as min$^{-1}$. © 2003 American Physiological Society. All rights reserved.
venting via the Eustachian tube is an early response to the rapidly developing ME overpressures, it is doubtful that those requirements are met during the time between onset of breathing the anesthetic gas mixture and first tubal opening. Therefore, the use of these analytic methods is best reserved for the experimental setting. There, anesthesia can be induced by a route independent of breathing mixture, sufficient periods of time can be allotted for acclimation to the anesthetized condition (allowing for the reequilibration of the physiological gases between ME and blood and stabilization of body temperature), and the N₂O composition of the breathing mixture can be adjusted to prevent the rapid development of ME overpressures that force Eustachian tube openings.

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