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

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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.

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 and 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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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 N\textsubscript{2}O (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 N\textsubscript{2}O 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 quantify the results in terms of a transmucosal time constant. In this paper, blood-to-ME exchange of N\textsubscript{2}O 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 N\textsubscript{2}O 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) 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 Harvard respirator (model 661; South Natick, MA). The endotracheal tube was placed on-line to the output of a Harvard respirator (model 661; South Natick, MA). The animal was breathed with room air for 60 min. Then the intake to the respirator was switched to the 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) 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 Harvard respirator (model 661; South Natick, MA). The respirator was adjusted to deliver 30 ml gas/stroke at 40 strokes/min. The animal was breathed with room air for 60 min. Then the intake to the respirator was switched to the experimental gas mixture, and the animal was breathed for 60 min with X% N\textsubscript{2}O, 20% O\textsubscript{2}, balance N\textsubscript{2} at ambient pressure, where X = 10, 20, and 20% for sessions 1, 2, and 3, respectively. Throughout the 120 min of respirator-controlled breathing, ME pressure was recorded bilaterally at 5-min intervals by use of a clinical tympanometer (GSI-33 middle ear analyzer, model 1733, Littleton, MA). Vital signs and rectal temperature were recorded at regular intervals. At the termination of the experimental session and after the monkey had recovered from the anesthesia, it was returned to the vivarium. This study was performed in accordance with the Public Health Service Policy on Humane Care and Use of Laboratory Animals, the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and the Animal Welfare Act (7 U.S.C. et seq.). The protocol was approved by the Animal Care and Research Committee at the Children’s Hospital of Pittsburgh.

Model description. Under certain restrictive conditions, the primary outcome variable for these experiments, change in ME pressure, is equal to the change in ME N\textsubscript{2}O pressure. Below we present a mathematical description that defines these conditions and the methods for calculating the time constant for transmucosal N\textsubscript{2}O exchange.

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

\[
P^m = V^m \cdot R^m \cdot T^m\]

where \(P^m\) is pressure, \(V^m\) is volume, \(N^m\) 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., N\textsubscript{2}O). The change in total ME pressure is equal to the sum of the changes in the partial pressures of those gases, or

\[
\frac{\Delta P^m}{\Delta t} = \left( \frac{\Delta P_{\text{N}_2}}{\Delta t} + \frac{\Delta P_{\text{CO}_2}}{\Delta t} + \frac{\Delta P_{\text{N}_2O}}{\Delta t} + \frac{\Delta P_{\text{H}_2O}}{\Delta t} + \frac{\Delta P_{\text{N}_2O}^a}{\Delta t} \right)
\]

where \(P_{\text{N}_2O}^a\) is the partial pressure of a test gas. Under physiological conditions and at constant blood partial pressures for O\textsubscript{2} and CO\textsubscript{2}, the ME-blood partial-pressure gradient for O\textsubscript{2} and CO\textsubscript{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, \(\frac{\Delta P_{\text{N}_2O}}{\Delta t} = 0\) Torr/min. Thus, for the ME of an acclimated, anesthetized animal breathing gas mixtures containing N\textsubscript{2}O, Eq. 2 reduces to

\[
\frac{\Delta P^m}{\Delta t} = \left( \frac{\Delta P_{\text{N}_2O}}{\Delta t} \right)
\]

Direct measurements in monkeys show that the change in ME N\textsubscript{2}O 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\textsubscript{2}O exchange rate is 0 Torr/min, and Eq. 3 becomes

\[
\frac{\Delta P^m}{\Delta t} = \frac{\Delta P_{\text{N}_2O}^a}{\Delta t} \quad \text{(4)}
\]

In the experiments described here, the N\textsubscript{2}O pressure in the arterial blood is increased during controlled breathing with the gas mixtures. There, the change in the number of moles of N\textsubscript{2}O 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

\[
\Delta N_{\text{N}_2O}^a = (N_{\text{N}_2O}^a - N_{\text{N}_2O}^v)
\]

For blood (b), the number of moles of a gas is directly related to the partial pressure (\(P^b\)) and solubility (\(S^b\)) of the gas in blood and the extant, local blood volume (\(V^b\)), or for N\textsubscript{2}O

\[
N_{\text{N}_2O}^b = V^b \cdot P_{\text{N}_2O}^b \cdot S_{\text{N}_2O}^b
\]

Recognizing that N\textsubscript{2}O solubility is the same for arterial and venous blood \((S_{\text{N}_2O}^a = S_{\text{N}_2O}^v)\), substituting the expressions for pressure from Eq. 1 and 6 for moles of gas in Eq. 5 and rearranging terms yields

\[
\frac{\Delta P_{\text{N}_2O}^a}{\Delta t} = (RT^a \cdot S_{\text{N}_2O}^a) \cdot (P_{\text{N}_2O}^b - P_{\text{N}_2O}^v) \end{\text{Equation 7}}
\]

Dividing both sides of this equation by a time interval \(\Delta t\) and noting that by continuity \(V^a/\Delta t = V^v/\Delta t = \text{ME blood flow (Q^m)}\), yields

\[
\frac{\Delta P_{\text{N}_2O}^a}{\Delta t} = \left( R Q^m T^a \cdot S_{\text{N}_2O}^a \right) / \left( P_{\text{N}_2O}^v - P_{\text{N}_2O}^a \right)
\end{\text{Equation 8}}

Under the experimental conditions, the ME pressure of N\textsubscript{2}O must at all times be less than or equal to that of the local arterial and venous blood such that

\[
P_{\text{N}_2O}^a \leq P_{\text{N}_2O}^v \end{\text{Equation 9a}}
\]
or

\[-P_{N_2,O}^m \cong -P_{N_2,O}^v \]

Adding $P_{N_2,O}^m$ to both sides of Eq. 9b yields

\[P_{N_2,O}^m - P_{N_2,O}^v \cong P_{N_2,O}^m - P_{N_2,O}^v \]

or

\[F_{N_2,O}(P_{N_2,O}^m - P_{N_2,O}^v) = P_{N_2,O}^m - P_{N_2,O}^v \]

where $1 \cong F_{N_2,O} \cong 0$. Substituting the result from Eq. 10b into Eq. 8 and combining with Eq. 4 yields

\[\delta P_{N_2,O}^{v/m}/\delta t = \delta P_{N_2,O}^{v/m}/\delta t = (F_{N_2,O}RQmTmS_{N_2,O}^{v})(P_{N_2,O}^m - P_{N_2,O}^v)/(Vm)^{-1} \]

(11)

This equation relates the rate of change in ME pressure ($\delta P_{N_2,O}^{v/m}/\delta t$, determinable from experimental data) to the product of the extant arterial-ME $N_2O$ pressure gradient ($P_{N_2,O}^m - P_{N_2,O}^v$) determinable from experimental data; the general gas constant ($R$); the inverse of ME volume ($Vm^{-1}$, a constant); ME temperature ($Tm$, measured to be constant); $N_2O$ solubility in blood ($S_{N_2,O}^{v}$, a constant); local volume blood flow ($Qm$), and the ratio of arterial-venous $N_2O$ gradient to arterial-ME $N_2O$ gradient ($F_{N_2,O}$). If $Qm$ and $F_{N_2,O}$ 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

\[\delta P_{N_2,O}^{v/m}/\delta t) = F_{N_2,O}(RQmTmS_{N_2,O}^{v})(Vm)^{-1} \]

(12)

Note that violation of these assumptions (i.e., within-session changes in $Qm$ or $F_{N_2,O}$) will be reflected as a nonlinear relationship between the rate of ME pressure change ($\delta P_{N_2,O}^{v/m}/\delta t$) and gradient ($P_{N_2,O}^m - P_{N_2,O}^v$), 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 ($P_{N_2,O}^m$) is assumed to be constant and was estimated by multiplying the physiological blood $N_2O$ pressure ($\approx 570$ 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 ($P_{N_2,O}^m$) 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 [$G_{N_2,O}^{v/m}$] as given by

\[G_{N_2,O}^{v/m} = P_{N_2,O}^m - (P_{N_2,O}^{v/m} - P_{N_2,O}^{v/m}) \]

(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 $>99\%$, and consequently we accepted the regression slope as a reasonable estimate of the instantaneous rate of change in ME pressure, $\delta P_{N_2,O}^{v/m}/\delta t$.

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

\[K_{N_2,O}^m = (\delta P_{N_2,O}^{v/m}/\delta t)G_{N_2,O}^{v/m} \]

(14)
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% (A), 10% (B), and 20% (C) N₂O. 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 N₂O 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% N₂O 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 N₂O exchange. That slope (± standard error of the estimate) calculated by linear regression is reported 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 ≥ 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 N₂O composition of the breathing mixture with approximate rate ratios of 4.2:1 for experiments conducted using gas mixtures containing 20%, 10%, and 5% N₂O, respectively.

Figure 2 shows a scatterplot of the rate of change in ME pressure vs. the arterial-ME N₂O 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 N₂O pressure gradient. The time constant for transmucosal N₂O exchange was estimated as the ratio of the rate of ME pressure change to the respective N₂O 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 N₂O in the breathing mixture.

**DISCUSSION**

In these experiments, ME pressure showed a decrease attributable to decreasing body temperature...
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 for 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., PN2O,PN2O at t = 0 = PN2O,PN2O 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 f1 = 60N2O – G f1 = 0N2O)/G f1 = 0N2O × 100%] yielded average values of 0 ± 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 (Qm) 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 f1 = K f2(Sg1/Sg2) where K f1 and K f2 are the transmucosal time constants (K f1 measured, K f2 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 f1S f1/F f2S f2, which reduces to a ratio of gas solubilities if and only if F f1 = F f2. 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) = X K N2O' (F N2O S N2O/F N2O S N2O), or K N2 = X K N2', 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

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

<table>
<thead>
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<th>Monkey</th>
<th>Ear</th>
<th>Session 1</th>
<th>Session 2</th>
<th>Session 3</th>
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Values are given as min−1.
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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