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Oral Pseudoephedrine Decreases the Rate of Trans-mucosal Nitrous Oxide Exchange for the Middle Ear

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Abstract

Objective—Determine if oral pretreatment with a vasoconstrictor decreases the blood to middle-ear exchange-rate of the perfusion-limited gas, Nitrous Oxide (N₂O).

Study Design—Randomized, double-blind, crossover study.

Methods—Ten adult subjects with and 10 without past middle-ear disease completed paired experimental sessions, identical but for oral pretreatment with either pseudoephedrine HCL or lactose placebo. At each session, subjects were fitted with a non-rebreathing mask and breathed room air for 20 minutes (acclimation period), 50% N₂O:50% O₂ for 20 minutes (experimental period) and 100% O₂ for 10 minutes (recovery period). Throughout, heart-rate, blood-pressure and O₂ saturation were monitored and bilateral middle-ear pressures were recorded by tympanometry every minute. The primary outcome was the slope of the middle-ear pressure-time function for the experimental period which estimates the volume N₂O exchange-rate. Using repeated measures ANOVA, the effects of Group (disease history), Treatment (active vs. placebo) and Period (1 vs. 2) on the recorded vital signs, and of Group, Treatment and Ear (left/right) on the middle-ear pressure-time slope were evaluated for statistical significance.

Results—Statistically significant effects of Period on O₂ saturation (Period 2>Period 1) and of Treatment on heart-rate (Active>Placebo) were documented. Only Treatment was statistically significant for the middle-ear pressure-time slope with a shallower slope characterizing the active treatment session.

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Conclusion—The volume exchange-rate across the middle-ear mucosa of perfusion-limited gases can be modulated pharmacologically. Theoretically, similar drugs can be used to reduce the requisite Eustachian tube opening efficiency for adequate middle-ear pressure regulation.

Keywords

adults; N₂O breathing; middle ear; pressure-regulation; decongestants; modeling

Introduction

Middle-ear (ME) pressure-regulation (MEPR) is a homeostatic mechanism that maintains the ME-ambient pressure-gradient within a narrow, zero-centered, range that maximizes hearing and preserves ME health¹. Hearing acuity is diminished as the absolute value of that gradient increases and, because the ME mucosal tissue-pressure tracks local ambient pressure, large negative ME-ambient pressure-gradients cause vascular disruption with leakage, mucosal inflammation and fluid accumulation within the normally gas-filled ME^{2,3}, a pathology not different from the clinical expression of otitis media with effusion (OME)⁴. Thus, the “risk” for certain types of hearing losses and ME pathologies is indirectly related to MEPR efficiency¹.

The ME is a usually closed, relatively fixed-volume, temperature-stable, gas-pocket. ME pressure is governed by the ideal gas law, $P^{ME} = RT^{ME}(V^{ME})^{-1}\sum^s n_s^{ME}$, and the rate of pressure change by the time-derivate of that equation, $\delta P^{ME}/\delta t = RT^{ME}(V^{ME})^{-1}\sum^s \delta n_s^{ME}/\delta t$, where P^{ME} , T^{ME} and V^{ME} are the ME pressure, temperature and volume, R is a gas constant, n_s^{ME} is species-moles, t is time, $\sum^s$ indicates summing over all represented species and δ denotes change¹. Physiologically, ME pressure is changed by processes that change its species-moles and, specifically, by passive gas-transfers between the ME and adjacent compartments².

The ME simultaneously exchanges gas-species with its local blood by diffusion across the ME mucosa (transMEM exchange), the ambient environment by diffusion across the tympanic membrane (transTM exchange) and the cochlear fluids by diffusion across the round window membrane (transRWM exchange)². The rates for these exchanges is given by Fick's law of diffusion, $Q_{\text{barrier}_s} = CK_{\text{barrier}_s} P_{\text{barrier}_s}$, where Q_{barrier_s} is trans-barrier volume gas-flow, C is a “moles to volume” scaling-constant, K_{barrier_s} is the species-conductance for the barrier, and P_{barrier_s} is the trans-barrier species pressure-gradient. Measurement shows that the transTM and transRWM species-conductances are negligibly small compared to the respective transMEM conductances^{5,6}. Moreover, the only physiologically extant species-gradient to drive transMEM gas-exchange is the ME-blood N₂ gradient of approximately 600 daPa since the ME-blood gradients for the other represented species, O₂, CO₂ and H₂O, are well-buffered at close to 0 daPa^{7,8}. Therefore, of the ME exchange pathways, only transMEM N₂ exchange satisfies the conditions for inter-compartment gas-exchange prescribed by Fick's diffusion equation and the net direction, magnitude and rate of pressure-change for the closed ME under physiologic conditions are solely determined by the transMEM N₂ conductance and pressure-gradient. For N₂ and other inert-gases (e.g. N₂O), the transMEM exchange-rate is perfusion-limited⁹⁻¹² such that species-conductance is

proportional to the volume-blood flow-rate per tissue-volume (i.e. the perfusion-rate), Q^{blood} , and species-solubility in the mucosa, S^{mucsa} , or: $K^{\text{mucsa}} = Q^{\text{blood}} S^{\text{mucsa}}$. Consequently, the equilibrium pressure for a closed ME is equal to the ambient pressure minus the ME-blood N_2 gradient ($\approx P^{\text{ambient}} - 600$ daPa) and the rate of ME pressure decrease to equilibrium is equal to the product of a scaling constant, the extant ME-blood N_2 gradient, the mucosal perfusion-rate and the transMEM N_2 conductance¹. Therefore, the rate, but not magnitude, of pressure-change for a closed-ME can be modulated by effecting changes in the mucosal blood perfusion-rate^{13,14}.

Periodic and transient, muscle-assisted Eustachian tube (ET) openings establish a gas-phase communication between the ME and nasopharynx (NP). Non-zero ME-NP (=ME-ambient) pressure-gradients at the time of ET openings drive a bolus gas-flow between the compartments according to the Hagen-Poiseuille equation, $Q^{\text{ET}} = K^{\text{ET}}_g P^{C1-C2}_g$, which relates the transET volume-gas flow-rate, Q^{ET}_g , to the product of the transET gas-conductance, K^{ET}_g , and pressure-gradient, P^{C1-C2}_g ². These gas-flows quickly change ME, but not ambient, pressure and, thereby, decrease the pre-opening, absolute value of the ME-ambient pressure-gradient. The efficiency of this ET pressure-equilibrating function can be expressed as the fractional ME-ambient pressure-gradient equilibrated per swallow (FGE), which is proportional to transET gas-conductance and ET opening duration, but independent of pressure-gradient¹⁵.

From these considerations, MEPR represents a time-limited balance in the ME volume-gas influx (V^{ME}_g) associated with ET openings and the volume- N_2 efflux ($V^{\text{ME}}_{N_2}$) attributable to gradient-driven N_2 transfer from the ME to local blood¹. For periods of stable ambient pressure, MEPR efficiency is directly related to the $V^{\text{ME}}_g/V^{\text{ME}}_{N_2}$ ratio. Experiments show that disrupting that ME gas-balance by decreasing ET efficiency (i.e. lowering V^{ME}_g)^{3,16,17}, increasing ME to blood volume gas-transfer (i.e. raising $V^{\text{ME}}_{N_2}$)¹⁸, or both causes ME pressure-dysregulation (MEPD) expressed as the sequential development of negative ME-ambient pressure-gradients, conductive hearing-loss and, at a ME-ambient pressure-gradient of about -250 daPa, ME mucosal inflammation and OME^{17,18}.

In persons with MEPD not caused by conditions that abolish transET gas-exchange (i.e. $V^{\text{ME}}_g=0$), the “risk” for these pathologies can be lessened by interventions that increase the $V^{\text{ME}}_g/V^{\text{ME}}_{N_2}$ ratio. To that end, one relatively simple strategy is to effect a decrease in ME gas-efflux by pharmacologically lowering the ME mucosal perfusion-rate. This would effectively decrease the requisite volume-gas influx (i.e. the frequency of ET openings and constitutive FGE) needed to stabilize the ME-ambient pressure-gradient at near 0 daPa (i.e. establish a $V^{\text{ME}}_g/V^{\text{ME}}_{N_2}$ ratio of 1). Here, the feasibility of that strategy is explored by creating a significant transMEM inert-gas pressure-gradient and determining the effect, if any, of a vasoconstrictive drug on the rate of ME pressure-change. The hypothesis tested is that the rate of ME pressure-increase in response to a positive transMEM blood-ME N_2O pressure-gradient is reduced by pretreatment with pseudoephedrine HCL (PDE)¹⁹.

Materials and Methods

Study Population

The protocol was approved by the IRB at the University of Pittsburgh. Healthy adults, recruited by advertisement, presented to the laboratory and signed an informed-consent for study participation. Consented subjects provided medical and surgical histories and a comprehensive history for ME diseases, comorbidities and predisposing conditions. They had an Ear Nose and Throat (ENT) examination with bilateral tympanometry (Titan, Eden Prairie, MN) and women had a urine pregnancy test (Consult Diagnostics hCG Dipstick, Jacksonville, FL). Pregnant women and persons with lactose intolerance or a past adverse reaction to breathing gas-mixtures containing N₂O, with chronic illness, who had taken prescription medication within the previous month (with the exception of birth control) or oral/nasal decongestants within the 2 weeks before either test session or with extant unilateral or bilateral OME or low tympanic membrane compliance or symptoms/signs of extant nasopharyngeal inflammation were excluded. The target population was 20 otherwise healthy adults, 10 with and 10 without past ME disease.

Protocol

The design was a randomized, double-blind, placebo-controlled, cross-over study requiring that participants complete paired N₂O breathing sessions at a minimum 1-week interval. At each session, the subject reported to the research clinic, provided an interval history for medication use, ME disease and upper respiratory diseases and had a brief ENT examination to verify continued eligibility, was pretreated with a double-blinded, oral medication (identical appearing capsules containing either 60 mg of immediate-release PDE or lactose) and, then, escorted to the Dental Clinic. There, the subject was seated in a reclined examination chair and fitted with: the finger probe of a pulse oximeter (Massimo RDS1), the cuff of an automated blood-pressure monitor (Critikon Dynamap 1846SX) and an appropriately sized Rudolph Nasal & Mouth Breathing Silicone Face Mask (Model 8900, Kansas, USA) with a two-way non-rebreathing valve. The delivery system supplying the mask was configured such that three gas sources could be placed “on-line”; room-air, a N₂O gas-mixture (50% O₂, 50% N₂O) or 100% O₂.

The experiment was begun 1 to 1.5 hours after dosing and consisted of a 20-minute acclimation period (Period 1, room-air breathing), a 20-minute experimental period (Period 2, gas-mixture breathing) and a 10-minute recovery period (Period 3, 100% O₂). Throughout, bilateral ME pressures were recorded by tympanometry at 1-minute intervals, blood O₂ saturation and heart-rate were monitored continuously and recorded every 5 minutes, and blood-pressure was measured and recorded every 5 minutes. At the end of Period 3, the subject was observed for 20 minutes, given a brief physical examination and was free to leave the clinic when recovered from breathing the N₂O gas-mixture. At least 1-week later, these procedures were repeated and the subject was dosed with the crossover capsule.

Pharmacology

PDE is a member of the phenethylamine and amphetamine chemical classes with direct and indirect sympathomimetic actions²⁰. Peak plasma concentrations are achieved between 1 and 2 hours^{21,22} peak salivary concentrations between 2 and 4 hours²³ and vasoconstrictive effects from 30 minutes to 4 hours after a single oral dose of 60 mg immediate-release PDE¹⁹. N₂O is a colorless, odorless gas that is highly soluble in blood and other tissues. On breathing, N₂O substitutes for N₂, rapidly achieves blood-alveolar equilibrium pressure²⁴ and exhibits a perfusion-limited trans-mucosal exchange-rate²⁵.

Data Analysis

A randomization code was submitted to a pharmacist who prepared the 2 pretreatments as identical looking capsules supplied to the investigators in sealed bottles labeled by session and subject number. Personnel were blinded to the code until all recordings were double-entered into a computer data-file, reconciled and locked to change.

For each session, the average blood O₂ saturation, heart-rate and systolic and diastolic blood-pressure were calculated for Periods 1 and 2 and the rate of increase in ME pressure was calculated for Period 2^{25,26}. There, ME pressure-time functions were analyzed independently by 2 blinded-investigators to calculate the slope of a linear segment representative of the change in ME pressure per change in time ($\delta P^{ME}/\delta t$) during the last 15 minutes of Period 2. Paired slope-estimates were compared, discrepancies reconciled and the average slopes used in the analysis.

The effects of Group, Treatment, Period and the Treatment by Group Interaction on blood O₂ saturation, heart-rate and systolic and diastolic blood-pressure, and the effects of Treatment, Group, Ear (right/left) and the Treatment by Group Interaction on the ME pressure-time slope were evaluated for significance using repeated measures ANOVAs (NCSS 2007 statistical package, Kaysville, Utah).

Results

Twenty-six subjects were screened, 3 disqualified and 23 enrolled. Twenty subjects (average age=26.7±8.8 years; 11 Males; 13 white, 6 black and 1 mixed race) completed the 2 test-sessions. For Group-1, 6 of the 10 subjects reported repeated episodes of ME effusion, 8 reported 3 or more episodes of “ear-ache” treated with antibiotics and 8 reported ventilation tube insertion(s) during childhood. Most (8/10) had outgrown their disease by late childhood, but 1 had ear problems into adolescence (13 years) and 1 (white female, aged 30.1 years) reported episodes of OME continuing into adulthood. No Group-2 subject reported past OME or other ME diseases. Four subjects in each group had nasal allergy, none asthma and 1, in Group-1, gastro-esophageal reflux disease.

There was a significant difference among individuals in all 4 vital signs measures ($P<0.001$) and a significant, but clinically irrelevant, effect of Group on systolic blood-pressure (Group-1=116 vs. Group-2=107 mmHg; $P=0.040$) and heart-rate (Group-1=68.5 vs. Group-2=60.6 BPM; $P=0.047$), of Period on O₂ saturation (Period 1=99.3% vs. Period

2=99.9%; $P<0.001$), and of Treatment on heart-rate (Placebo=62.3 vs. Active=67.1 BPM; $P=0.001$).

The Table reports the results for the ANOVA operating on the slopes of the ME pressure-time function. Those slopes were significantly different among individuals and between Treatments. The adjusted average slopes were 6.21 ± 2.21 and 4.81 ± 2.21 daPa/min for the placebo and PDE pretreatments. There was no effect of Group, Ear or the Interaction on this variable.

Figure 1 shows a scatterplot of the ME pressure-time slopes for the PDE pretreatment as a function of the paired-slopes for the placebo pretreatment. The majority of points lay below the identity line for the placebo pretreatment documenting lesser values for the PDE pretreatment. As shown in Figure 2, the ME pressure-time slopes for the right and left ears of individuals were related linearly. The fit of the regression line between right and left slopes was significantly better for the placebo pretreatment (Right Slope = $0.12 \times$ Left Slope + 0.78; $r^2=0.72$) when compared to the PDE pretreatment (Right Slope = $0.71 \times$ Left Slope + 1.76; $r^2=0.26$).

Discussion

For normal auditory function, ME gas-pressure needs to be maintained at near-ambient levels. However, isolated, biological gas-pockets such as the ME are not stable at ambient pressure but exhibit either a progressive volume-collapse or, if rigid, an exponential pressure decrease to approach the tissue gas-pressure of about ambient-600 daPa^{27,28}. The anatomical construction of the ME allows for both of these behaviors, wherein ME pressure first exhibits a progressive decrease to a mucosa-ME hydrostatic pressure-gradient of about -250 daPa and, then, the ME gas-space shows a volume-collapse as vascular fluids accumulate to displace the ME gas-volume¹. In healthy MEs, this fate is avoided by periodic ET openings which establish short-duration, ME-NP gas-phase communications and permit gradient-driven ME-NP gas-flow which resets ME pressure at near-ambient levels. This process represents a homeostatic mechanism to preserve a near-zero ME-ambient pressure-gradient, MEPR, with ET opening being the sole pressure-regulator and diffusive ME to blood N₂ transfer being the primary driver of gradient instability.

The opposing processes of MEPR operate over different time-scales. Specifically, ME volume gas-efflux is continuous for relatively long time-periods between ET openings (measured in minutes to hours) and ME volume gas-influx is a discrete event occurring during a tubal opening (average duration $\approx$ 400 msec)²⁹. Thus, the $V^{iME}_g/V^{eME}_{N_2}$ ratio exhibits a temporal pattern characterized by successive values of 1 bounding variable-length periods during which the ratio decreases. Because ME pressure is governed by the ideal gas law, these changes are reflected as changes in ME pressure and, at stable environmental pressure, changes in the ME-ambient pressure-gradient. Adequate MEPR requires that the sum of accumulated ME volume-gas gain and loss is 0 ul (i.e. $V^{iME}_g/V^{eME}_{N_2}=1$) at a time, t^e , within all time-intervals, t^p , where t^e is the time between each occurrence of $V^{iME}_g/V^{eME}_{N_2}=1$ and t^p is the time required for ME gas-volume efflux to drive the ME-ambient pressure-gradient to the critical-level that causes pathology in a specified ME. Thus, MEPR

efficiency can be quantified as the t^p/t^e time-ratio with higher ratios reflecting greater efficiencies and ratios less than 1 defining MEPR. Because an individual's "risk" for conductive hearing-loss and certain ME pathologies is inversely related to MEPR efficiency³⁰, interventions that effect an increase in the t^p/t^e time-ratio will decrease those risks and, perhaps, promote resolution of existing pathologies.

The t^p/t^e time-ratio can be increased by increasing t^p , decreasing t^e or both. Past approaches to modulating MEPR efficiency focused almost exclusively on decreasing t^e by pharmacological/surgical interventions intended to improve ET efficiency, but with limited success³¹. Here, the feasibility of the alternative strategy to increase the t^p/t^e time-ratio was explored. Because t^p measures the time required for the extant rate of ME volume gas-loss to precipitate pathology, it is inversely related to the transMEM N_2 exchange-rate that, in turn, depends on the mucosal blood perfusion-rate. Consequently, it was hypothesized that pharmacological interventions that decrease the perfusion-rate would decrease the transMEM N_2 exchange-rate, extend t^e , and increase the t^p/t^e time-ratio

That hypothesis was tested using a previously developed²⁵ and field-tested^{26,32} experimental protocol capable of estimating the transMEM N_2 exchange-rate from measured values of the transMEM N_2O exchange-rate. A formal mathematical description of the blood-ME species-exchanges under this protocol documented the correspondence between the measured variable (i.e. slope of the ME pressure-time function) and the parameter to be estimated (i.e. transMEM N_2 conductance) as well as the validity of using the surrogate gas, N_2O , to estimate the transMEM N_2 exchange-rate^{1,25,26,32}. N_2O was used as the test gas because it exhibits a perfusion-limited transMEM exchange-rate that is approximately 33 times faster than the N_2 rate³³ which allows the required measurements to be made within a "reasonable" time-period. The active treatment, PDE, was chosen for its known mucosal vasoconstrictive effects¹⁹. Because the transMEM N_2O exchange-rate depends on mastoid geometry^{26,32}, a cross-over design was used and the trans-MEM N_2O exchange-rate was compared between placebo and active treatments within ears/persons.

The results support the tested hypothesis that the rate of ME pressure-increase in response to a positive transMEM blood-ME N_2O pressure-gradient is decreased by pretreatment with PDE and, by implication, support the validity of the underlying assumptions applicable to this setting. The latter include: 1) oral PDE at the specified dose causes a significant ME mucosal vasoconstriction for a duration sufficient to include the time-period when the measurements were made, and 2) this vasoconstriction is expressed as a significant decrease in the ME mucosal blood perfusion-rate. Because the transMEM exchange-rates for both N_2O and N_2 are governed by the same perfusion-limited exchange-equation, it is expected that PDE and other pharmacological modulators of blood perfusion will have predictable effects on the transMEM N_2 exchange-rate and, consequently, MEPR efficiency. From the effect size for this experiment, it is expected that dose of PGE used will increase MEPR efficiency by about 33%. Experiments are ongoing in our laboratory to test these expectations.

A few studies reported that ET efficiency was poorer for otherwise healthy MEs with past ME disease when compared to ears without past disease^{34,35}. Extant inflammation with/

without ME fluid is associated with an increased transMEM inert-gas exchange-rate presumably due to an increased volume-blood perfusion-rate for inflamed mucosa^{12,36,37}. However, the possible effect of disease history on transMEM inert-gas exchange-rates has not been explored. In this study, persons with and without past ME disease were enrolled but the analysis identified no significant effect of disease history on the measured trans-MEM N₂O exchange-rate. However, the power to detect expected differences was low given the sample size of 10 subjects/group. Thus, this remains an unresolved question to be evaluated more rigorously in future studies.

As an aside, a significant left-right correlation in the magnitudes of the trans-MEM N₂O exchange rates was documented. Given the results of previous studies showing rate dependence on mastoid geometry²⁶, this correlation may reflect a bilateral symmetry in ME geometry for those enrolled. If supported by future experiments, there may be a basal level of trans-MEM N₂ exchange-rate fixed by ME geometry and other factors. In turn, variations in this could affect the degree of achievable pharmacological modulation of the trans-MEM N₂ exchange-rate and thereby restrict the expected benefit of using vasoconstrictors as a “treatment” to improve MEPR efficiency to subgroups pre-selected on the basis of their basal exchange-rate.

Conclusion

Oral administration of a vasoconstrictive drug decreased the transMEM N₂O exchange-rate. Because all inert-gases are characterized by a perfusion-limited transMEM exchange-rate, this effect is expected to extend to the transMEM N₂ exchange-rate which is the primary determinant of the requisite ET efficiency for adequate MEPR. Modulating ME mucosal blood-perfusion can increase MEPR efficiency but, alone, cannot stabilize ME pressure at near-ambient levels.

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References

1. Doyle, W. Middle ear pressure regulation. In: Rosowski, J.; Merchant, S., editors. *The Function and Mechanics of Normal, Diseased and Reconstructed Middle Ears*. The Hague, The Netherlands: Kugler Publications; 2000.
2. Kanick SC, Doyle WJ. Barotrauma during air travel: predictions of a mathematical model. *J Appl Physiol* (1985). May; 2005 98(5):1592–1602. [PubMed: 15608090]
3. Casselbrant ML, Cantekin EI, Dirksmaat DC, Doyle WJ, Bluestone CD. Experimental paralysis of tensor veli palatini muscle. *Acta Otolaryngol.* Sep-Oct;1988 106(3-4):178–185. [PubMed: 3176963]
4. Bluestone CD, Doyle WJ. Anatomy and physiology of eustachian tube and middle ear related to otitis media. *J Allergy Clin Immunol.* May; 1988 81(5 Pt 2):997–1003. [PubMed: 3286738]

5. Yuksel S, Douglas Swarts J, Banks J, Doyle WJ. CO(2) gas exchange across the human tympanic membrane is not appreciably affected by pathology. *Eur Arch Otorhinolaryngol.* Feb; 2011 268(2): 203–206. [PubMed: 20809264]
6. Yuksel S, Swarts JD, Banks J, Seroky JT, Doyle WJ. In vivo measurement of O(2) and CO(2) gas exchange across the human tympanic membrane. *Acta Otolaryngol.* Jul; 2009 129(7):716–725. [PubMed: 18728916]
7. Hergils L, Magnuson B. Human middle ear gas composition studied by mass spectrometry. *Acta Otolaryngol.* Jul-Aug;1990 110(1-2):92–99. [PubMed: 2386039]
8. Hergils L, Magnuson B. Middle ear gas composition in pathologic conditions: mass spectrometry in otitis media with effusion and atelectasis. *Ann Otol Rhinol Laryngol.* Sep; 1997 106(9):743–745. [PubMed: 9302904]
9. Doyle WJ, Alper CM, Seroky JT. Trans-mucosal inert gas exchange constants for the monkey middle ear. *Auris Nasus Larynx.* Jan; 1999 26(1):5–12. [PubMed: 10077250]
10. Doyle WJ, Alper CM, Seroky JT, Karnavas WJ. Exchange rates of gases across the tympanic membrane in rhesus monkeys. *Acta Otolaryngol.* Jul; 1998 118(4):567–573. [PubMed: 9726685]
11. Doyle WJ, Seroky JT. Middle ear gas exchange in rhesus monkeys. *Ann Otol Rhinol Laryngol.* Aug; 1994 103(8 Pt 1):636–645. [PubMed: 8060059]
12. Doyle WJ, Seroky JT, Alper CM. Gas exchange across the middle ear mucosa in monkeys. Estimation of exchange rate. *Arch Otolaryngol Head Neck Surg.* Aug; 1995 121(8):887–892. [PubMed: 7619416]
13. Seroky JT, Alper CM, Tabari R, Doyle WJ. Effects of intranasal challenge with histamine, bradykinin and prostaglandin on middle ear pressure and blood flow in cynomolgus monkeys. *Acta Otolaryngol.* Jan; 1995 115(1):83–87. [PubMed: 7762391]
14. Yuksel S, Doyle WJ, Banks J, Seroky JT, Alper CM. Nasal prostaglandin challenge increases N2O exchange from blood to middle ear. *Auris Nasus Larynx.* Mar; 2005 32(1):29–32. [PubMed: 15882822]
15. Swarts JD, Casselbrant ML, Teixeira MS, et al. Eustachian tube function in young children without a history of otitis media evaluated using a pressure chamber protocol. *Acta Otolaryngol.* Jun; 2014 134(6):579–587. [PubMed: 24828350]
16. Casselbrant ML, Doyle WJ, Cantekin EI, Ingraham AS. Eustachian tube function in the rhesus monkey model of cleft palate. *Cleft Palate J.* Jul; 1985 22(3):185–191. [PubMed: 3860312]
17. Alper CM, Tabari R, Seroky JT, Doyle WJ. Magnetic resonance imaging of the development of otitis media with effusion caused by functional obstruction of the eustachian tube. *Ann Otol Rhinol Laryngol.* May; 1997 106(5):422–431. [PubMed: 9153108]
18. Swarts JD, Alper CM, Seroky JT, Chan KH, Doyle WJ. In vivo observation with magnetic resonance imaging of middle ear effusion in response to experimental underpressures. *Ann Otol Rhinol Laryngol.* Jul; 1995 104(7):522–528. [PubMed: 7598363]
19. Stubner UP, Toth J, Marks B, Berger UE, Burtin B, Horak F. Efficacy and safety of an oral formulation of cetirizine and prolonged-release pseudoephedrine versus xylometazoline nasal spray in nasal congestion. *Arzneimittelforschung.* 2001; 51(11):904–910. [PubMed: 11765592]
20. Johnson DA, Hricik JG. The pharmacology of alpha-adrenergic decongestants. *Pharmacotherapy.* 1993; 13(6 Pt 2):110S–115S. [PubMed: 7507588]
21. Simons FE, Gu X, Watson WT, Simons KJ. Pharmacokinetics of the orally administered decongestants pseudoephedrine and phenylpropanolamine in children. *J Pediatr.* 1996; 129(5): 729–34. [PubMed: 8917241]
22. Kanfer I, Dowse R, Vuma V. Pharmacokinetics of oral decongestants. *Pharmacotherapy.* 1993; 13(6 Pt 2):116S–128S. [PubMed: 7507589]
23. Strano-Rossi S, Leone D, de la Torre X, Botrè F. Analysis of stimulants in oral fluid and urine by gas chromatography-mass spectrometry II: pseudoephedrine. *J Anal Toxicol.* 2010; 34(4):210–5. [PubMed: 20465867]
24. Evers, AS.; Crowder, CM. General anesthetics. In: Hardman, JG.; Limbird, LE.; Gilman, AG., editors. *The pharmacological basis of therapeutics.* New York, NY: McGraw-Hill; 2001. p. 337-365.

25. Doyle WJ, Banks JM. Middle ear pressure change during controlled breathing with gas mixtures containing nitrous oxide. *J Appl Physiol* (1985). Jan; 2003 94(1):199–204. [PubMed: 12486021]
26. Alper CM, Kitsko DJ, Swarts JD, et al. Role of the mastoid in middle ear pressure regulation. *Laryngoscope*. Feb; 2011 121(2):404–408. [PubMed: 21271597]
27. Van Liew HD, Schoenfisch WH, Goldberg MM. Diffusion of oxygen from gas pockets to capillaries. *Microvasc Res*. Apr; 1969 1(3):257–265. [PubMed: 5406307]
28. Burkard ME, Van Liew HD. Simulation of exchanges of multiple gases in bubbles in the body. *Respir Physiol*. Feb; 1994 95(2):131–145. [PubMed: 8191036]
29. Alper CM, Swarts JD, Singla A, Banks J, Doyle WJ. Relationship between the electromyographic activity of the paratubal muscles and eustachian tube opening assessed by sonotubometry and videoendoscopy. *Arch Otolaryngol Head Neck Surg*. Aug; 2012 138(8):741–746. [PubMed: 22801708]
30. Bluestone, CD. Eustachian Tube Structure, Function, Role in Otitis Media. Hamilton, Ontario: BC Decker Inc; 2005.
31. Swarts JD, Alper CM, Luntz M, et al. Panel 2: Eustachian tube, middle ear, and mastoid--anatomy, physiology, pathophysiology, and pathogenesis. *Otolaryngol Head Neck Surg*. Apr; 2013 148(4 Suppl):E26–36. [PubMed: 23536530]
32. Doyle WJ. The mastoid as a functional rate-limiter of middle ear pressure change. *Int J Pediatr Otorhinolaryngol*. Mar; 2007 71(3):393–402. [PubMed: 17174408]
33. Doyle WJ, Alper CM, Banks JM, Swarts JD. Rate of nitrous oxide exchange across the middle ear mucosa in monkeys before and after blockage of the mastoid antrum. *Otolaryngol Head Neck Surg*. May; 2003 128(5):732–741. [PubMed: 12748569]
34. Teixeira MS, Banks J, Swarts JD, Alper CM, Doyle WJ. Eustachian tube opening measured by sonotubometry is poorer in adults with a history of past middle ear disease. *Int J Pediatr Otorhinolaryngol*. Apr; 2014 78(4):593–598. [PubMed: 24491807]
35. Swarts JD, Alper CM, Mandel EM, Villardo R, Doyle WJ. Eustachian tube function in adults without middle ear disease. *Ann Otol Rhinol Laryngol*. Apr; 2011 120(4):220–225. [PubMed: 21585150]
36. Alper CM, Doyle WJ, Seroky JT. Higher rates of pressure decrease in inflamed compared with noninflamed middle ears. *Otolaryngol Head Neck Surg*. Jul; 1999 121(1):98–102. [PubMed: 10388887]
37. Doyle WJ, Alper CM. A model to explain the rapid pressure decrease after air-inflation of diseased middle ears. *Laryngoscope*. Jan; 1999 109(1):70–78. [PubMed: 9917044]

Figure 1.

Scatterplot of the ME Pressure-Time slopes recorded after active pretreatment as a function of the paired slopes recorded after the placebo pretreatment for Group-1 (history of middle ear disease - open circles) and Group-2 (controls - open squares). The solid line is the line of identity for the placebo slopes.

Figure 2.

Scatterplot of ME Pressure-Time slopes recorded for the right ears as a function of the paired slopes recorded for the left ears after the placebo (open circles) and active (open squares) pretreatments. The solid line is the line of identity for the left ear slopes.

ANOVA for the ME Pressure-Time Slopes listing the sources of variation and, for each source, the associated degrees of freedom (df), sum of squares (SSQ), mean square (MSQ), F-Ratio and probability level (P-Value).

Table

Source	df	SSQ	MSQ	F-Ratio	P-Value
Group	1	9.86	9.86	0.28	0.606
Individual	18	645.54	35.86	7.17	0.000
Ear	1	0.15	0.15	0.03	0.865
Treatment	1	39.49	39.49	7.90	0.007
Group × Treatment	1	0.14	0.14	0.03	0.867
Error	57	284.93	5.00		
Total (Adjusted)	79	980.11			
Total	80				