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THE MASTOID AS A FUNCTIONAL RATE-LIMITER OF MIDDLE EAR PRESSURE CHANGE

William J. Doyle, Ph.D.

Department of Otolaryngology, University of Pittsburgh School of Medicine

Abstract

INTRODUCTION—The physiological function of the mastoid air cell system (MACS) with respect to middle ear (ME) pressure-regulation remains controversial because predictive mathematical models and experimental data to formulate and test hypotheses are lacking.

OBJECTIVE—A mathematical description of MACS volume effects on the rate of ME pressure change is presented; the agreement between published data and model prediction is examined for consistency with the hypothesis that the MACS acts as a functional rate-limiter of ME pressure change, and an explanation for the relationship between MACS volume and otitis media is discussed.

METHODS—The mathematical description shows that the value of a single, free parameter, termed the “MACS buffering efficiency” (M) determines if MACS volume affects the rate of ME pressure change caused by diffusive gas exchange. The MACS serves no rate-limiting function for $M=0$, acts as a gas sink for $M>1$ and acts as a gas reserve (rate-limiter) for $M<1$.

RESULTS—Fitting the model equation to published adult human data yielded an estimate for M of 0.2. This implies that larger MACS volumes are associated with lesser rates of change in ME pressure caused by diffusive gas exchange and lesser required frequencies of effective Eustachian tube openings to maintain near ambient ME pressures.

CONCLUSION—If well-controlled studies confirm $M<1$ for children and adults, larger MACS volumes will increase the time required to develop sufficient ME underpressures to cause otitis media by *hydrops ex vacuo* during transient or prolonged periods of Eustachian tube dysfunction.

Keywords

mastoid volume; rate-limiting function; middle ear pressure-buffering; mathematical modeling

INTRODUCTION

The mastoid air cell system (MACS) is a multiply partitioned airspace located within the petrous bone posterior to and in communication with the airspace of the tympanum [1,2]. Developmentally, the MACS shows an age-related increase in volume to exceed that of the tympanum by fold magnitudes in adults. Previous studies reported that children with small MACS volume had significantly more episodes of otitis media and otitis media episodes of longer duration when compared to age-matched controls with large MACS volume, and other studies reported that adults with small MACS volume were at higher risk for otitis media during upper respiratory infections when compared to those with large MACS volume [3–7]. This linkage between MACS size and predisposition to middle ear (ME) disease has been interpreted

as evidencing directional causality with either small MACS volume predisposing to otitis media or, alternatively, with otitis media stunting the expansion of MACS volume during growth [2,4,7–11].

To date, there is no clear resolution as to which, if either, of these interpretation is correct. Experimental studies using animals are not feasible since, with the exception of higher primates that have a prolonged period of growth and development, most species used in ME research have an inflated ME bulla rather than a MACS [12]. Moreover, the physiological function(s), if any, of the MACS is not known though a number of hypotheses have been advanced. These include active gas generation and ME pressure-buffering. While the physiological mechanism underlying MACS gas generation is not well developed [3,5,13] and experimental evidences supporting that possibility have alternative explanations [14], ME pressure-buffering is easily demonstrated. There, pressure-buffering can be decomposed into two effects, a magnitude-limiting effect on pressure change under conditions where ME cavity volume is changed (Boyle's Law) [15] and a rate-limiting effect on pressure change under conditions where the contained volume of ME gas is changed (General Gas Law) [16]. Confusion between the consequences of changing ME volume and changing ME gas volume is common in the published literature and this underlies much of the existing controversies regarding the functional role of the MACS in ME pressure-regulation [4,17]. ME pressure-regulation refers to those physiological processes that compensate for or minimize the effects of external and internal factors that disturb the ME-ambient pressure equilibrium required for maintaining good hearing levels and an uninflamed ME mucosa.

In this paper, the ME pressure-buffering effects of the MACS as a magnitude and a rate-limiter of pressure change are discriminated, a mathematical description for determining if the MACS acts as a rate-limiter of ME pressure change is developed, the hypothesized rate-limiting function of the MACS is tested against published data [18], and a contextual consideration of the results is used to explain the relationship between MACS volume and otitis media risk.

METHODS

Mathematical Description of MACS Volume Effects on ME Pressure

For any time (t), the general gas law relates the gas pressure (P) in the ME cavity (e) to its extant volume (V), temperature (T) and contained gas moles (N) as:

$$P^e = N^e R T^e (V^e)^{-1} \text{ or } P^e = \Sigma N_g^e R T^e (V^e)^{-1} \quad \text{EQ1a}$$

where ΣN_g^e is the sum of moles over all contained gases (g). Under physiological conditions, ME temperature is constant and ME volume can be decomposed into the sum of tympanum and MACS volumes, such that

$$P^e = \Sigma N_g^e C^e (V^m + V^t)^{-1}, \quad \text{EQ1b}$$

where C^e is a constant representing the product of the general gas constant R and ME temperature. Two independent factors can effect ME pressure change; changing ME volume ($V^m + V^t$) and/or changing the contained number of gas moles (ΣN_g^e). The relevant equations describing these effects are the respective derivatives of EQ1b (Note that throughout, “/” indicates conditions that are extant, and “k” indicates that those conditions are constant),

$$\delta P^e = -\Sigma N_g^e C^e P^e \delta V^e (V^e)^{-1} \quad // \delta N^e, \delta T^e = 0, \text{ and} \quad \text{EQ2a}$$

$$\delta P^e = C^e (V^m + V^t)^{-1} \delta \Sigma N_g^e \quad // \delta V^e, \delta T^e = 0. \quad \text{EQ2b}$$

In strict sense, EQ2a is applicable only to conditions wherein the volume of the “closed” (i.e. no gas entry, exit or production) ME is changed situationally as, for example, during displacements of the tympanic membrane in ears with a closed Eustachian tube. There, identical volume displacements will cause greater ME pressure changes for those MEs with lesser initial volumes; i.e. MACS volume acts as a magnitude-limiter of ME pressure change [19]. This phenomenon is a valid physical property of all similarly constructed pressure systems but, with few isolated exceptions conditioned by an extremely high ratio of tympanic membrane displacement volume to total ME volume (e.g. hyper-compliant tympanic membrane in a low volume ME can protect from barotitis or delay the onset of ME pressure change caused by diffusive, transmucosal gas exchange [15]), is not relevant to explaining the relationship between MACS volume and otitis media risk. In contrast, EQ2b describes the effect on ME pressure of adding or removing gas to a ME system with fixed volume as for example during diffusive gas exchange between the ME and adjacent compartments (See Below). The time derivative,

$$\delta P^e / \delta t = C^e (V^m + V^t)^{-1} \Sigma \delta N_g^e / \delta t \quad // V^e, T^e = k, \quad \text{EQ3}$$

describes the rate of change in ME pressure as a function of the rate of change in contained gas moles for a fixed volume ME, and the validity of the hypothesis that the MACS acts as a rate-limiter of ME pressure change depends on whether or not this relationship is conditioned on MACS volume. To appreciate this, it is necessary to assign a value to the rate of change in ME gas moles ($\Sigma \delta N_g^e / \delta t$) based on a consideration of gas flow (Q^P) across all pathways linking the ME to its adjacent compartments: i.e. gas exchange with the nasopharynx via the Eustachian tube; the atmosphere via the tympanic membrane, the inner ear via the round window and the local blood via the ME mucosa.

Because the Eustachian tube is usually closed, gas transfers require muscle-assisted openings [20,21]. For an individual ear, volume gas flow ($Q^{ET} = \delta N / ET \text{ opening}$) is a function of the extant total pressure gradient and the values of relatively fixed structural and functional parameters of the Eustachian tube [15]. From EQ3, the change in ME pressure effected by each Eustachian tube opening is an inverse function of ME volume and a direct function of volume gas flow that, in turn, depends on the above listed factors. Because the major influences affecting MACS volume are age and disease history and these also relate to the efficiency of trans-Eustachian tube gas exchange (e.g. greater age is associated with both greater MACS volumes and more efficient volume gas transfers), it is difficult to predict the effect of MACS volume on this component of ME pressure-regulation.

In contrast, the pathways linking the ME to the other three compartments are characterized by bidirectional, gas-species dependent, diffusional flows (Q^{Path_g}). There, for times between Eustachian tube openings, EQ3 can be rewritten for the fixed-volume, temperature stable ME as:

$$\delta P^e / \delta t = C^e (V^m + V^t)^{-1} \Sigma^{\text{path}} \Sigma^g Q^{\text{path}}_g \quad // V^e, T^e = k; Q^{\text{ET}} = 0 \quad \text{EQ4a}$$

where Σ^{path} indicates summing across the three passive exchange routes. This equation can be simplified by noting that gas exchange across the round window and the tympanic membrane at physiological pressure-gradients is extremely slow when compared to gas transfers across the ME mucosa [22,23]. Consequently, as a first approximation, it is assumed that the total rate of ME pressure change is attributable to the exchange rate across the MACS and tympanum mucosa, and EQ4a reduces to:

$$\delta P^e / \delta t = C^e (V^m + V^t)^{-1} \Sigma^g (Q^m_g + Q^t_g) \quad // V^e, T^e = k; Q^{\text{ET, TM, RW}} = 0. \quad \text{EQ4b}$$

Also, under physiological conditions and at constant blood O_2 and CO_2 pressures, the transmucosal partial-pressure gradient for those gases is approximately 0 mmH₂O and the ME is saturated with water vapor [24,25]. Because there is no gradient to drive gas exchange, $Q^{m,t}_{O_2} = Q^{m,t}_{CO_2} = Q^{m,t}_{H_2O} = 0$ moles/min, and EQ4b reduces to:

$$\delta P^e / \delta t = C^e (V^m + V^t)^{-1} (Q^m_{N_2} + Q^t_{N_2}) \quad // V^e, T^e = k; Q^{\text{ET, TM, RW}} = 0, Q^{m,t}_{g \neq N_2} = 0. \quad \text{EQ4c}$$

Under EQ4c, the quantity of N_2 transferred to the ME must be equal to the extant difference between the arterial N_2 moles on entering the ME mucosa and the venous N_2 moles exiting the ME mucosa (i.e. $\delta N^e_{N_2} = N^a_{N_2} - N^v_{N_2}$) which can be written as N_2 flow rates across the MACS and tympanum mucosa by taking the time derivative of the relationship, or:

$$Q^m_{N_2} = \delta(N^{ma}_{N_2} - N^{mv}_{N_2}) / \delta t \text{ and } Q^t_{N_2} = \delta(N^{ta}_{N_2} - N^{tv}_{N_2}) / \delta t. \quad \text{EQ5a}$$

The number of moles of an inert gas in blood is the product of gas partial-pressure ($P^b_{N_2}$), gas solubility in blood ($S^b_{N_2}$, equal for arterial and venous blood) and blood volume (V^b), and substituting this relationship into EQ 5 yields:

$$Q^m_{N_2} = S^b_{N_2} \delta(P^{ta}_{N_2} V^b - P^{tv}_{N_2} V^{bv}) / \delta t \text{ and } Q^t_{N_2} = \delta(P^{ma}_{N_2} V^{ma} - P^{mv}_{N_2} V^{bv}) / \delta t. \quad \text{EQ5b}$$

This set of equations can be simplified by recognizing that the arterial N_2 pressure is identical for MACS and tympanum mucosa, that the change in blood volume per unit time is blood flow (Q_b) and that, by continuity, the venous and arterial blood flows are equal for each compartment (no blood pooling in mucosa of tympanum or mastoid) which yields the paired equations:

$$Q^m_{N_2} = S^b_{N_2} Q^m_b (P^a_{N_2} - P^{tv}_{N_2}) \text{ and } Q^t_{N_2} = S^b_{N_2} Q^t_b (P^a_{N_2} - P^{mv}_{N_2}). \quad \text{EQ5c}$$

Substituting this result into EQ4c and simplifying yields:

$$\delta P^e / \delta t = C^e S^b_{N_2} (V^m + V^t)^{-1} [Q^m_b (P^a_{N_2} - P^{tv}_{N_2}) - Q^t_b (P^a_{N_2} - P^{mv}_{N_2})] // V^e, T^e = k; Q^{\text{ET, TM, RW}} = 0, Q^{m,t}_{g \neq N_2} = 0. \quad \text{EQ6a}$$

Under physiological conditions, the ME pressure of N_2 is at all times greater than or equal to that of the local arterial and venous blood, i.e. $P^e_{N_2} \geq P^v_{N_2} \geq P^a_{N_2}$ [25,26]. From this it follows

that $P_{N_2}^a - P_{N_2}^v \geq P_{N_2}^a - P_{N_2}^e$ and a constant of proportionality ($F_{N_2}^e$) can be chosen such that $(P_{N_2}^a - P_{N_2}^v) = F_{N_2}^e(P_{N_2}^a - P_{N_2}^e)$. Also, experimental studies and theoretical calculations show that air-phase gas exchange is extremely rapid *vis a vis* exchange across the mucosa [6, 27] such that gas partial pressures are approximately equal in the two ME compartments, i.e. $P_{N_2}^e \sim P_{N_2}^m \sim P_{N_2}^t$. Substituting these results into EQ 6a and simplifying yields the final equation for the rate of change in ME pressure caused by diffusive transmucosal gas exchange,

$$\delta P^e / \delta t = C^e S_{N_2}^b (V^m + V^t)^{-1} (P_{N_2}^a - P_{N_2}^e) (Q_{N_2}^m F_{N_2}^m + Q_{N_2}^t F_{N_2}^t) // V^e, T^e = k; Q^{ET, TM, RW} = 0, Q_{g \neq N_2}^{m, t} = 0. \quad \text{EQ6b}$$

Model Application to MACS as a Rate-Limiter of ME Pressure Change

The inclusion of possible differences in regional blood flow as controlling factors governing ME pressure change caused by diffusive gas exchange complicates the simple relationship between ME pressure-regulation and MACS volume suggested by others. To appreciate this, note that total volume blood flow for either the MACS or tympanum compartment (c) can be decomposed as follows: $Q_c^b = (Q_c^b / A^c) (A^c / V^c) V^c$ where A^c and V^c are the surface area and volume of the compartment. Then, Q_c^b / A^c is the average blood flow per unit surface area ($R_{Q/A}^c$) and A^c / V^c is the surface area-volume ratio ($R_{A/V}^c$). For the MACS, these parameters, with volume and the proportionality constant can be written in terms of the respective values for the tympanum such that: $F_{N_2}^m = U F_{N_2}^t$, $V^m = X V^t$, $R_{Q/A}^m = Y R_{Q/A}^t$ and $R_{A/V}^m = Z R_{A/V}^t$, where U, X, Y and Z are scaling constants. Substituting these relationships into EQ 6b and simplifying yields:

$$\delta P^e / \delta t = C^e S_{N_2}^b (V^m + V^t)^{-1} (P_{N_2}^a - P_{N_2}^e) V^t Q_{N_2}^t F_{N_2}^t (1 + XM), // V^e, T^e = k; Q^{ET, TM, RW} = 0, Q_{g \neq N_2}^{m, t} = 0 \quad \text{EQ7}$$

where M is the product of the scaling constants Y, Z, and U ($M = YZU$). For the non-inflamed ME, the product $C^e S_{N_2}^b (V^m + V^t)^{-1} (V^t Q_{N_2}^t F_{N_2}^t)$ is valued as a constant and, therefore, the rate of ME pressure change is a function of the arterial-ME N_2 pressure gradient and the structural geometry of the ME represented by $1 + XM$, where X is the number of equivalent tympanum volumes summed to equal MACS volume and M is the average effective perfusion rate *vis a vis* the tympanum over all equivalent volumes. M is referred to as the MACS buffering coefficient and its value is the single determinant whether or not the MACS functions as a rate-limiter for ME pressure change.

Relationship Between the Time-Constant for Transmucosal Gas Exchange and M

A time-constant ($K_{N_2}^e$) for transmucosal N_2 exchange can be calculated as the ratio of the rate of change in ME pressure to the driving gradient, such that

$$K_{N_2}^e = (\delta P^e / \delta t) / (P_{N_2}^a - P_{N_2}^e) = C^e S_{N_2}^b (V^m + V^t)^{-1} V^t Q_{N_2}^t F_{N_2}^t (1 + XM). \quad \text{EQ8a}$$

The term $(V^m + V^t)$ can be rewritten as $V^t(X+1)$ and EQ 8a can be simplified as:

$$K_{N_2}^e = C^e S_{N_2}^b Q_{N_2}^t F_{N_2}^t (1 + XM)(X+1)^{-1} = C^{e'} (1 + XM)(X+1)^{-1} \quad \text{EQ8b}$$

where $C^{e'}$ is the product of the constants C^e , $S_{N_2}^b$, $Q_{N_2}^t$ and $F_{N_2}^t$. As represented, the time-constant is independent of the units of measure and extant driving gradients since it has the units of time^{-1} (e.g. $\text{mm H}_2\text{O/sec/mm H}_2\text{O} = \text{/sec}$). EQ8b shows that the time constant for N_2 exchange is dependent only on certain properties of the gas, ME geometry and the value

of the MACS buffering coefficient, M . The time-constant is also useful to standardize exchange rates when comparing the volume exchange of different inert gases across the same pathway (See below for N_2O to N_2 conversion) or of the same inert gas across different pathways [16, 22,28].

Hypothesis Testing

To test the hypothesis that the MACS is a rate-limiter of ME pressure change (i.e. serves as a gas reserve), it is necessary to measure the value of M for transmucosal N_2 exchange. The hypothesis can be rejected for all $M \geq 1$ and supported for all $M < 1$, i.e. for all conditions where the volume rate of gas loss/volume is greater for the tympanum when compared to the MACS. Note that a simple physical model explaining this relationship without the cumbersome mathematics was previously published and the reader is referred to that publication for a more descriptive presentation [29].

Practically, measurement of M is made difficult by the extremely slow transmucosal N_2 exchange rate and the subsequent need to maintain a closed ET for long measurement periods, conditions that are not easily maintained in laboratory experiments [28]. However, EQ8b is equally valid for any inert gas (i.e. gases characterized by perfusion limited transmucosal exchange). Previously, a significant increase in ME pressure was reported for anesthetized patients breathing gas mixtures that included N_2O [7,30] and one study reported paired data for pneumatized MACS area and the rate of change in ME pressure during 50% N_2O breathing in adult subjects [18]. Like N_2 , N_2O is an inert gas whose rate of exchange across the ME mucosa is primarily perfusion limited [28]. For strict application of the model equation to the N_2O data, it is necessary to show that, like the other physiological gases, the rate of N_2 exchange is effectively 0 mm H₂O/min over the time course of the experiment. This is a reasonable assumption for the conditions of the N_2O experiment reported by Elam and colleagues, given the short duration of the measurement period and the results of past studies that showed the transmucosal time-constant for N_2O to be orders of magnitude greater than that for N_2 ($K_{N_2O}^e \gg K_{N_2}^e$) [16,28].

To model their experiment and provide an estimate of M for adult humans, it is necessary to recover from the presented data paired estimates of the rate of change in ME pressure, the driving N_2O gradient and the volume of the ME (tympanum+MACS), other model parameters can be considered to be constant across ears/experiments. For each subject, the rate of change in ME pressure ($\delta P^e/\delta t$) and pneumatized MACS area (proportional to MACS volume) were reported. Because all subjects breathed the same gas mixture at a controlled ventilation rate and the initial (physiological) N_2O pressure in the ear is 0 mm H₂O, the maximum blood-ME N_2O gradient at arterial saturation is estimated to approximate 5000 mm H₂O [16,28] and the gradient decay can be estimated as the difference between that value and the total increase in ME pressure during the experiment (<40 mm H₂O). This shows that the N_2O gradient (G_{N_2O}) can be assumed to be constant within and between experiments. EQ 8b can then be rewritten as a simple and predictable relationship between the ratio the rate of change in ME pressure ($\delta P^e/\delta t$) at a specified N_2O gradient (G_{N_2O}) which equals the N_2O time-constant, a representation of MACS geometry (the scaling constant, C^e), the number of equivalent tympanum volumes represented by MACS volume (X) and the MACS buffering coefficient M , or

$$K_{N_2O}^e = C^e (1 + XM) / (1 + X). \quad \text{EQ8c}$$

To estimate M , the MACS buffering coefficient for the human ME, the developed equation was fitted to the data for the study described by Elam and colleagues [18] after appropriate choice of a scaling constant. For curve fitting, it should be noted that the time-constant equals

C and approaches M at the two limiting MACS volumes (0 or $\rightarrow \infty$; to confirm this, substitute these values for X into EQ8c and solve for $K_{N_2O}^e$).

RESULTS

Using the simple model equation (EQ8c), the effect of MACS volume on the time-constant for transmucosal exchange of an inert gas, g was simulated at different values of the MACS buffering coefficient, M. For all simulations, the gas gradient (G_g , a constant) and the scaling constant (C^e) were assigned a value of 1 and the predicted transmucosal time-constant for the gas ($K_{g_g}^e$) was plotted as a function of relative MACS volume (multiples of tympanum volume). The results presented in Figure 1a show that: for $M=1$, MACS volume has no effect on the time-constant; for $M>1$, increasing MACS volume causes increasing values of the time-constant, and for $M<1$, increasing MACS volume causes decreasing values of the time-constant, i.e. lesser rates of transmucosal gas transfers at specified partial-pressure gradients, the characteristic of a pressure rate-buffer. As shown in Figure 1b, the curve for the function relating a normalized measure of the time-constant ($K_{g_g}^{e'}$, calculated as $(K_{g_g}^e - M)/(C^e - M)$) to normalized MACS volume is identical at all $M<1$. Importantly, for any value of M, 50% of the maximum effect of MACS volume on the time-constant is achieved at 1, 66% at 2 and 75% at 3 equivalent tympanum volumes. This shows that the MACS rate-buffering effect on ME pressure change is a diminishing function of increasing MACS volume such that a high fraction of maximal buffering effect is realized at relatively small MACS volume (*vis a vis* that of the tympanum).

To provide an estimate of M for adult human MEs, the model equation was fitted to the reported data for the study by Elam and colleagues under the assumption that all ears were sampled from a population with the same value of M. There, three free parameters needed to be estimated: the value of the scaling constant (C^e), the functional relation between pneumatized MACS area (measured) and volume, and the value of M. As a first approximation, the N_2O time-constants ($K_{N_2O}^e$) calculated for the two extremes of pneumatized MACS area in the population were identified and the scaling constant was estimated by the value of time-constant at a MACS volume of (approaches in the limit) 0 units (see previous section) and M was estimated as the absolute value of the difference between those time-constants divided by the estimate of scaling constant (i.e. maximum MACS volume effect on $K_{N_2O}^e$ divided by the measured $K_{N_2O}^e$ at 0 volume). The transform (MACS area to volume) multiplier was then chosen to alter the abscissa scale for best fit to the study data. Note that because the equation has more than one free parameter, an exact solution cannot be obtained, though, a family of related solutions can be defined. Shown in Figure 2 are a scatterplot of the data collected by Elam and colleagues and one fitted model solution (parameters: $C^e=30$, multiplier=0.5, $M=0.20$). While there are clearly a number of outliers (demarcated as filled circles), the overall fit of the model equation was good. Importantly, because the form of the data distribution is not consistent with model predictions for $M\geq 1$ (see Figure 1a), the hypothesis that the MACS acts to buffer the rate of ME pressure change caused by diffusive gas exchange, i.e. is a functional pressure rate-limiter, is supported. While an exact value of M cannot be derived from the existing data, such a determination would be useful in specifying the MACS buffering “efficiency” for the population, with lesser values corresponding to higher efficiencies.

A functional interpretation of the value of M with respect to ME pressure-regulation requires an appreciation of the scaling relationship between the N_2O ($K_{N_2O}^e$, surrogate inert gas used for measurement of M) and N_2 time-constants ($K_{N_2}^e$, physiological inert gas that controls the rate of ME pressure change) and of the effect of the N_2 time-constant on ME pressure change for time intervals between Eustachian tube openings. Regarding the former, EQ8a shows that for a given ME with a specified geometry, the N_2 time-constant can be written as a linear function of the N_2O constant [$(K_{N_2}^e = K_{N_2O}^e S_{N_2}^b F_{N_2}^t (S_{N_2O}^b F_{N_2O}^t)^{-1}$ or $K_{N_2}^e = R K_{N_2O}^e$, where

R is a scaling constant]. Thus, any linear operation on either of the two time-constants is true for the other. As to the latter, EQ7 shows that the rate of change in ME pressure is equal to the N_2 time-constant multiplied by the extant ME-blood N_2 pressure gradient. Using this equation, predicted ME pressure (ref. ambient) as a function of time was calculated for 4 representative values of the N_2 time-constant (.05, .025, .015 and .005/time; ratio 1, .5, .3 and .1) and the results are shown in Figure 3a. All four functions have a similar general form (curvilinear decrease to -600 mm H_2O in the limit where $P_{N_2}^e = P_{N_2}^a$), but lesser values of the time-constant are associated with lesser rates of ME pressure change. Consequently, for $M < 1$, increased mastoid volume causes decreased values of the N_2 time-constant, which in turn, causes lesser rates of ME pressure change.

This interpretive model may explain the protective effect of larger MACS volumes with respect to otitis media. There, past studies showed that at a specified ME underpressure (≤ -300 mm H_2O , ref ambient), the capillaries within the ME mucosa hemorrhage, the ME mucosa becomes permeable to passive fluid exchange and submucosal fluids are transferred to the ME airspace where they accumulate as an effusion [31–33]. The critical time (interval between successive Eustachian tube openings required to achieve pathological underpressure by transmucosal N_2 exchange) was calculated from the model equation using the N_2 time-constant estimated for $M=0.2$ and was plotted as a function of relative MACS volume (See Figure 3b). The form of the function shows that: the critical time is increased with increasing MACS volume; the slope of the function (change in critical time per change in MACS volume) decreases with increasing MACS volumes, and the critical time at the upper limit of MACS volume ($= \infty$) is 5 times greater than that for the lower limit of MACS volume (0 units), or, more generally, the maximum critical time is $1/M$ times the minimal critical time. Because the critical time is an inverse measure of the required frequency of effective Eustachian tube openings needed to resupply gas to the ME, these results show that the parameter M for a population contains information related to the minimal frequency of effective Eustachian tube openings required to prevent pathology.

DISCUSSION

Over more than 40 years, evidence has accumulated showing a linkage between a small MACS volume and a positive history for ME disease, but the responsible mechanism is still debated [1–5,7–9,¹¹,13,15,34,35] While some have argued with experimental support that ME infection, otitis media and/or poor Eustachian tube function prevent the normal growth and development of the MACS, others suggested that small MACS predispose to otitis media by disturbing ME pressure-regulation (i.e. generating conditions that favor the development of underpressures sufficient to cause mucosal pathology). While the results presented here cannot be used to support or refute the former position, they do provide a mathematical foundation for understanding the effect of MACS volume on ME pressure-regulation.

In that regard, the possible effects of MACS volume on ME pressure has had confusing presentations in the literature with most describing a limiting effect of large MACS volume on the total magnitude of ME pressure change. For example, in explaining the protective role for a large MACS in preventing otitis media, Sade and Fuchs wrote: “The physiological role of the pneumatized MACS can be seen to be a function of its volume, which according to Boyle’s law, may share and damp ME pressure aberrations”, p39 [9]. As discussed in the Methods Section, Boyle’s law is applicable to the change in pressure for a given ear during fluctuations in cavity volume but is not relevant to comparisons across MEs with different total volumes and where ME pressure change is primarily effected by diffusive gas exchange. A MACS magnitude-limitation on ME pressure change erroneously implies that larger MACS volumes will maintain stable ME pressures at lesser deviations from ambient when compared to smaller MACS volumes. This expectation is not consistent with known physiological mechanisms of

diffusive gas exchange where, in the absence of gas supply from an external source, ME pressure will be stable only when the blood-ME pressure gradients for all represented gases are equal to 0 mm H₂O. Because the sum of the blood gas partial-pressures is less than that of the ambient environment by approximately 600 mm H₂O [24,25], ME pressure will be stable at that underpressure irrespective of MACS volume (See Figure 3a).

Alternatively, the MACS could buffer the rate of ME pressure change effected by diffusive, transmucosal gas transfers. Because the total ME-blood pressure gradient under physiological conditions is attributable to the difference in N₂ pressure, a rate-limiting function for the MACS would be manifest as a lesser rate of transmucosal N₂ exchange for larger MACS. The developed equations show that this is true only true for ears derived from a population where the tympanum/MACS ratio of effective blood perfusion (related to surface area) per unit volume, M, is less than 1. Geometrical considerations show that the surface area per unit volume ratio of the MACS is much greater than that for the tympanum, and consequently, if M<1, blood perfusion per unit surface area must be much less for the MACS when compared to the tympanum [1,14,37–39].

In vivo measurement of the parametric contributors to M is not easily done, but the developed model equation makes verifiable predictions for the effect of M on the form of the function relating the rate of ME pressure change at established arterial-ME inert gas pressure gradients (the time-constant) to relative MACS volume (See Figure 1). The results of an earlier experiment designed to estimate the value of M in cynomolgus monkeys, a species characterized by a MACS similar to humans, could not exclude M=1, i.e. no effect of MACS volume on the rate of ME pressure change [16]. In this report, the relevant equation was fitted to a data set published for adult humans breathing gas mixtures containing 50% N₂O and one solution included an estimated M of 0.2 (See Figure 2) [18]. Moreover, the overall form of the data distribution for the experiment appeared to exclude M≥1 implying a rate-limiting function for the MACS with respect to ME pressure change caused by diffusive gas exchange. If the estimate of .2 (or any value of M<1) is reproducible in future experiments, MEs with larger MACS will be characterized by lesser rates of pressure decrease secondary to transmucosal N₂ exchange and will require lesser frequencies of effective Eustachian tube openings for gas resupply to the ME, i.e. more efficient pressure-regulation.

The value of M estimated here assumes that M is fixed for sequentially added MACS volumes, that M is a constant in the population of adult ears sampled and that tympanum blood flow is independent of MACS volume (See EQ8 for effect of changing Q on K_g^e). Violation of the first two assumptions could introduce large errors into the estimate but would also significantly alter the form of the predicted function relating ME pressure change to relative MACS volume. The general agreement between the predicted from of the function and the experimental data suggests that those assumptions are valid for the modeled population of adults. However, because these relationships must be maintained during the period of growth and development, they are too restrictive to allow for extension of any conclusions to the pediatric population.

The last assumption is more troublesome to data interpretation since increased mucosal perfusion which is directly related to the value of the time-constant for inert gas exchange is a common feature of inflammation and MACS volume has been related to diseases characterized by ME inflammation [33,40]. Thus, when distributed within a population of ears, increased mucosal perfusion associated with residual inflammation or subclinical disease in ears with small MACS would impose a relationship between the time-constant and MACS volume that mimics the function predicted for M<1, i.e. higher values for the time-constants at lower relative MACS volumes and lower values at greater MACS volumes. Indeed, the outliers in Figure 2 lying above the model prediction may represent a variant of this phenomenon wherein undiagnosed, perhaps transient, ME mucosal inflammation increased the N₂O time-constant

relative to that for the more usual, uninflamed state. For these reasons, while suggestive of a rate-limiting effect of MACS volume on ME pressure change, the study reported by Elam and colleagues should be repeated with better control over the extant inflammatory state of the mucosa (e.g. by MRI validation of a disease-free state) for all MEs to eliminate this possible source of error.

If indeed the value of M is less than one for the human ME, does this provide an explanation for the relationship between MACS volume and otitis media? As noted above, in the absence of Eustachian tube openings, the value of M has no relevance to the terminal ME pressure at equilibrium with blood, but does affect the rate of ME pressure change in response to established ME-blood pressure gradients. For $M < 1$, the absolute value of M defines the maximum effect of MACS volume on the rate of ME pressure change, while for any given value of M , the major impact of increasing MACS volume is confined to relatively few volume multiples of the tympanum (i.e. efficient rate-buffering does not require exceedingly large mastoid volumes *vis a vis* tympanum volume). Accepting that ME pathology develops at ME underpressures on the order of -300 mm H₂O, $M < 1$ predicts that larger MACS volumes will allow for longer times without effective Eustachian tube openings before disease is provoked. Such an effect is supported by past reports of a protective effect of large MACS volumes with respect to otitis media in adults during viral upper respiratory tract infections [9]. There, it could be argued that the viral infection caused a transient Eustachian tube dysfunction in most ears, but otitis media only in those ears where the underpressure associated with mucosal pathology was achieved prior to resolution of the Eustachian tube dysfunction, an expectation for confined to ears with a high required frequency of Eustachian tube openings for gas resupply (i.e. those with smaller MACS volumes). This and related hypotheses that define the functional characteristics of ME pressure-regulation and the relationship between pressure-dysregulation and ME disease are being explored further in our laboratories.

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Figure 1.

a) Time-constant for ME pressure change effected by inert transmucosal gas exchange as a function of relative MACS volume for $M = 2, 1, .5$ and $.1$; and b) Relative time-constant for ME pressure change effected by diffusive gas exchange as a function of relative MACS volume for any ear with $M < 1$ (See text for explanation).

Figure 2.
Scatterplot of the rate of ME pressure change versus estimated MACS volume for the data reported by Elam and colleagues and one solution for the predicted function described by EQ8.

Figure 3.

a) Effect of varying the N_2 time-constant, $K_{N_2}^c$ on the predicted ME pressure (referenced to ambient) -time function for periods without Eustachian tube opening (from top to bottom, $K_{N_2}^c = .05, .025, .015$ and $.005/\text{time}$); and b) Relative time to achieve a ME underpressure of $-300 \text{ mm H}_2\text{O}$ (critical time) as a function of relative MACS volume for $M=0.2$.