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A formal description of middle ear pressure-regulation

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ABSTRACT

Introduction: Middle ear (ME) pressure-regulation (MEPR) is a homeostatic mechanism that maintains the ME-environment pressure-gradient (MEEPG) within a range optimized for "normal" hearing.
Objective: Describe MEPR using equations applicable to passive, inter-compartmental gas-exchange and determine if the predictions of that description include the increasing ME pressure observed under certain conditions and interpreted by some as evidencing gas-production by the ME mucosa.
Methods: MEPR was modeled as the combined effect of passive gas-exchanges between the ME and: perilymph via the round window membrane, the ambient environment via the tympanic membrane, and the local blood via the ME mucosa and of gas flow between the ME and nasopharynx during Eustachian tube openings. The first 3 of these exchanges are described at the species level using the Fick's diffusion equation and the last as a bulk gas transfer governed by Poiseuille's equation. The model structure is a time-iteration of the equation: $P^{ME}_{g(t=(i+1)\Delta t)} = \sum^{s}(P^{ME}_{s(t=i\Delta t)}+(1/(\beta^{ME}{}_{s}V^{ME})\sum^{P}(K^{P}_{s}(P^{C}_{s(t=(i\Delta t)}-P^{ME}_{s(t=(i\Delta t))}))$. There, $P^{ME}_{g(t=i\Delta t)}$ and $P^{ME}_{s(t=i\Delta t)}$ are the ME total and species-pressures at the indexed times, $P^{C}_{s(t=i\Delta t)}$ is the species-pressure for each exchange-compartment, $\beta^{ME}{}_{s}V^{ME}$ is the product of the ME species-capacitance and volume, K^{P}_{s} is the pathway species-conductance, and $\sum^{S}$ and $\sum^{P}$ are operators for summing the expression over all species or exchange pathways.
Results: When calibrated to known values, the model predicts the empirically measured ME species-pressures and the observed time-trajectories for total ME pressure and the MEEPG under a wide variety of physiologic, pathologic and non-physiologic conditions.
Conclusions: Passive inter-compartmental gas exchange is sole and sufficient to describe MEPR.

1. Introduction

The middle ear (ME) is a relatively non-collapsible, biological gas pocket that is usually closed to direct communication with the ambient environment (Sade and Ar, 1997). For hearing, the middle-ear (ME) functions to detect the near-continuous, low-magnitude, high-frequency, environmental pressure fluctuations associated with perceived "sound", represent that flux as a pressure-time signal conditioned for effective gas-fluid coupling and present the conditioned pressure-time signals to the cochlear perilymph (Hawkins, 1964; Mason, 2016; Wilson, 1987). The sensory unit for this mechanism, the tympanic membrane (TM), functions like the diaphragm of a differential pressure-sensor. Consequently, optimal signal extraction requires that the ME medium be matched to that of the environment (i.e., gas-gas coupling) and that the ME "reference" pressure be maintained at near atmospheric levels. However, those requisite conditions are intrinsically unstable as environmental pressure independently fluctuates with changes in altitude and the movement of weather fronts and ME pressure is independently changed by diffusive gas transfers between the ME and adjacent anatomical compartments (Doyle, 2000). A ME-environment mismatch in pressure and/or media dampens TM responsiveness causing a conductive "hearing loss".

In otherwise healthy MEs, hearing efficiency is inversely related to the absolute magnitude of the ME-environment gas-pressure gradient (MEEPG) measured at a standard ME volume (Austin, 1978; Lildholt, 1983; Tonndorf, 1964; Wright, 1970; Zwislocki and Feldman, 1970). Moreover, at an approximate MEEPG of −300 daPa, the accompanying mucosal-ME hydrostatic pressure gradient causes the ME gas pocket to "collapse" with fluids transferred from the local blood to the ME cavity (Alper et al., 1997; Flisberg, 1970; Swarts et al., 1995). That pathologic condition is

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associated causally with a moderate to severe conductive hearing loss (Dobie and Berlin, 1979; Roland et al., 1989).

Biological homeostasis is the maintenance of a quasi-stable physiologic state by mechanisms that counter those processes that drive a system toward instability and, ultimately, functional failure (Recordati and Bellini, 2004). For the ME, homeostasis refers to those mechanisms that maintain a negligible MEEPG (i.e. system regulators) by countering the effects of other processes that drive the development of non-zero MEEPGs (i.e. system stressors). This biofeedback mechanism is referred to as ME pressure-regulation (MEPR) (Doyle, 2000).

It is well accepted that the risks for certain types of conductive hearing loss and ME pathologies are inversely related to MEPR efficiency (Bluestone and Klein, 2007; Dobie and Berlin, 1979; Kitahara et al., 1994; Roland et al., 1989; Truswell et al., 1979). Consequently, there is a continuing interest in developing medical and/or surgical interventions that improve MEPR efficiency in certain "at risk" populations (Kanemaru et al., 2005, 2013, 2004; Llewellyn et al., 2014; Yung, 1998). In application, this requires that the physiology of MEPR be well understood from a mechanistic perspective. Currently, a number of conceptually distinct mechanisms for MEPR have been described, with stable MEEPGs being volume-regulated, temperature-regulated, pressure-regulated, flow-regulated or regulated by some combinations of these mechanisms (Adams, 1954; Bluestone, 2005; Csakanyi et al., 2014; Doyle, 2000; Fooken Jensen et al., 2016; Gaihede et al., 2010; Hergils and Magnuson, 1988; Paduariu et al., 2015).

Traditional descriptions of MEPR are based on a flow-regulated model that for efficient function requires a balance in the volume of gas supplied to the ME during Eustachian tube (ET) openings with the volume removed from the ME by passive trans-barrier diffusive exchange with adjacent compartments. Here, a formal, mathematical model of flow-regulated MEPR that incorporates standard equations for passive inter-compartmental gas-exchange is developed (Ranade et al., 1980) and then used to test the hypothesis that a flow-regulated description of MEPR is sole and sufficient to explain the behaviors of ME pressure known from observation and experiment. To that end, the model was parameterized and evaluated for accuracy in predicting the empirically measured ME gas composition and the MEEPG trajectories observed under physiologic and non-physiologic conditions. Included in the latter are those that favor an increasing ME pressure over short time intervals, a phenomenon often attributed to gas-production by the ME mucosa (MEM) (Buckingham, 1990; Buckingham and Ferrer, 1980; Kanemaru et al., 2004, 2005). Abbreviations and symbols used in the text and equations are presented in Table 1.

2. Theory

2.1. Exchange system structure

The functional ME is a temperature stable, relatively fixed-volume, gas-filled, bony cavity located within the petrosal portion of the temporal bone. That cavity is divided into two primary subcompartments, the anterior, ME proper and the posterior, mastoid air-cell system (MACS) (Bluestone, 2005). These subcompartments are continuous in the gas-phase via a fixed-diameter open channel, the mastoid antrum, and share a continuous mucosa consisting of a single layer of epithelial cells overlying a connective tissue matrix that embeds the arteries, veins and capillaries that support cellular metabolism. While the MACS volume is partitioned by mucosa covered bony septa into numerous gas-cells that communicate in the gas-phase, the ME proper is a single cell bridged by the 3 ossicles that condition and transmit externally applied forces (pressures) acting on the TM to the oval window of the cochlea. The TM, located along the lateral wall of that compartment, separates the ME from the ambient environment. The oval window, located along the medial wall of the compartment, is fully fitted with the bony footplate of the stapes and is one boundary of a fluid-filled (perilymph) cochlear channel that terminates at the round window membrane (RWM) posterior and inferior to the oval window. Anteriorly, the ME is continuous with the lumen of the Eustachian tube (ET), a biological tube that extends between the ME and nasopharynx (NP) (Bluestone and Klein, 2007).

The ET consists of a "cane-shaped" superio-medial cartilage that is completed laterally and inferiorly by a membrane. This framework encloses a thick mucosa that surrounds the ET lumen which is continuous with that of the ME and NP. The ET lumen is open at the ME but, throughout its course, is usually closed by a mucosal tissue-pressure greater than atmospheric pressure. The tensor veli palatini, a thin inverted-triangular muscle, takes origin from the lateral membranous wall of the ET (Rood and Doyle, 1978). Its fibers proceed laterally, inferiorly and anteriorly to converge as a tendon that rounds the hamulus to become continuous with the palatine aponeurosis. Contraction of that muscle during swallowing and other maneuvers by an as yet undefined action (e.g. yawning, jaw repositioning, etc.) actively opens the ET lumen (Cantekin et al., 1979a, 1979b). Also, the ET lumen is passively opened by the generation of NP (e.g. Valsalva maneuver) or ME pressures much greater than the periluminal pressures that hold the lumen closed (Doyle et al., 2013).

2.2. Definition of gas pressure

The gas species-pressure, P^{C}_{s}, for a compartment (C) containing gas in the gas-phase (G) or dissolved in a liquid (L) is equal to the

Table 1
Abbreviations used in text and symbols used in equations.

Abbreviations: ET-Eustachian Tube; EV-Expected Value; FGE-Fractional Gradient Equilibrated in 1 swallow; ME-Middle Ear; MEEPG-Middle Ear to Environment Pressure Gradient; MEM-Middle Ear Mucosa; MEPR-Middle Ear Pressure Regulation; NP-Nasopharynx; TM-Tympanic Membrane.
Compartment Symbols: $\beta^{C}_{s,g}$ -Capacitance Coefficient, C^{C}_{s} -Molar Concentration, $\eta^{C}_{s,g}$-moles, S^{C}_{s} -Solubility, T^{C} –Temperature (°K), $P^{C}_{s,g}$ –Pressure, V^{C} –Volume.
Barrier Symbols: A^{b} –Surface Area, $\beta^{b}_{s,g}$ –Capacitance Coefficient, D^{b}_{s} –Diffusivity-Coefficient, $F^{B/MEM}$ –Blood/Mucosa Volume Ratio, $K^{m}_{s,g}$ –Conductance, L^{b}_{d} –Diffusion Length, V^{b} –Volume, V^{rb} –Mucosal Blood Volume, Q^{rb}–Volume Blood Perfusion Rate.
Eustachian Tube Symbols: F^{ETO} –Frequency Eustachian Tube Openings, Δt^{ET}_{o} –Active Eustachian Tube Opening Time, K^{FGE}_{g} –Eustachian Tube Conductance Coefficient, P^{ETO}_{g} -Eustachian Tube Opening Pressure, P^{ETC}_{g} –Eustachian Tube Closing Pressure.
Exchange Symbols: t – Time, $\emptyset^{b}_{s}$ Species Flux–(moles/distance; time), $M^{C1\text{-}C2}_{s,g}$ – Inter-Compartmental Molar Exchange Rate (moles/time).
Operator Symbols: ‖ -Given, Δ -Difference, ∂ - Change, $\sum^{c}$ Sum Over Categories C,
$\boxtimes^{b}_{a}$ –Area Under the Curve from A to B.

Superscript specifies compartment (C), barrier (b), subscript references total gas (g) or species (s).