On morphometric measurement of oxygen diffusing capacity in middle ear gas exchange

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1Department of Pediatric Otolaryngology, Children’s Hospital of Pittsburgh; 2Department of Chemical and Petroleum Engineering, University of Pittsburgh; and 3Department of Otolaryngology, University of Pittsburgh School of Medicine, Pittsburgh; 4Department of Mechanical Engineering and Mechanics, Lehigh University, Bethlehem; and 5McGowan Institute for Regenerative Medicine, Pittsburgh, Pennsylvania

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Kanick, Stephen Chad, William J. Doyle, Samir N. Ghadiali, and William J. Federspiel. On morphometric measurement of oxygen diffusing capacity in middle ear gas exchange. J Appl Physiol 98: 114–119, 2005. First published August 13, 2004; doi:10.1152/japplphysiol.00203.2004.—An accurate mathematical model of transmucosal gas exchange is prerequisite to understanding middle ear (ME) physiology. Current models require experimentally measured gas species time constants for all extant conditions as input parameters. However, studies on pulmonary gas exchange have shown that a morphometric model that incorporates more fundamental physiochemical and anatomic parameters accurately simulates transport from which the species time constants can be derived for all extant conditions. Here, we implemented a variant of that model for ME gas exchange that requires the measurement of diffusional length (τ) for the ME mucosa. That measure contributes to the mucosal diffusing capacity and reflects the resistance to gas flow between air space and capillary. Two methods for measuring τ have been proposed: linear distance between the air-mucosal boundary and capillary and the harmonic mean of all contributing pathway lengths. Oxygen diffusing capacity was calculated for different ME mucosal geometries by using the two τ measures, and the results were compared with those predicted by a detailed, two-dimensional finite element analysis. Predictive accuracy was improved by incorporating the harmonic τ measure, which captures important information regarding variations in capillary shape and distribution. However, compared with the oxygen diffusing capacity derived from the finite element analysis, both measures yielded nonlinear, positively biased estimates. The morphometric techniques underestimate diffusion length by failing to account for the curvilinear gas flow pathways predicted by the finite element model.

diffusion length; mathematical model; finite element analysis

THE MIDDLE EAR (ME) cleft is a relatively noncollapsible body cavity consisting of an air space encapsulated by mucosa-covered bone. As depicted in Fig. 1A, the normal ME mucosa is a simple epithelium overlying a thin submucosa interspersed with capillaries. Because the ME air space is usually isolated from the ambient environment, transmucosal gas exchange will drive total ME air space pressure to equilibrium with the summed blood pressures of the physiological gases, a deficit of ~50 Torr when referenced to ambient pressure (5). Physiologically, that magnitude of underpressure is not realized. There, periodic and transient muscle-assisted openings of the Eustachian tube (ET) allow for gradient driven, bolus exchanges of nasopharyngeal and ME gases that, in turn, reduce the total, preexisting ME-ambient pressure difference. Should ET openings fail to supply a sufficient quantity of gas to balance the volume gas loss by transmucosal exchange, the maximum underpressure is limited by the hydrostatic tissue pressure, which, at a relative ME underpressure of ~25 Torr (reference ambient), causes capillary leakage, fluid transudation into the mucosa, and the substitution of effusion for air in the ME cavity (1). This pathological condition, referred to as otitis media with effusion (OME), impairs the normal transduction function of the ME, resulting in a moderate to severe conductive hearing loss (4).

Although ET function under normal and pathological conditions has been well studied (3), the demand placed on the ET for gas resupply is poorly understood (5). There, because of the relative inaccessibility of the relevant compartments to measurement (e.g., ME mucosa, local blood, ME air space, etc.), experiments provide only an indirect measure of transmucosal gas-exchange parameters, and the resulting data need to be interpreted by using mathematical models of the exchange processes (7). In that regard, the most well-developed models are compartmental in nature and require as primary input parameters either direct or indirect measurement of species gas-exchange constants. Although predictive of ME pressure behavior under a variety of conditions (6, 8, 9), the underlying mechanism(s) must be inferred from agreement between model prediction and experiment and is not easily related to physiology. Ideally, a complete mathematical model of ME transmucosal gas exchange would require as inputs only the physiochemical properties of the physiological gases (e.g., gas species diffusivity, solubility in tissue/blood, etc.) and the geometric relationships for the exchange system (capillary distribution, mucosal thickness, surface area, etc.). There, the bulk exchange constants used in the compartmental models would be emergent quantities of these more fundamental parameters.

Fink and colleagues (12) recently developed a refinement to these compartmental models, in which they calculated the ME mucosal diffusing capacity (Dm), i.e., the effective barrier resistance to gas flow. This model has the advantage of relying on known physiological transport parameters and accepted geometrical relations while eliminating the need for artificially constructed parameters. However, their model assumes a constant area-thickness ratio of the mucosal diffusion barrier, calculated from empirical exchange data. Incorporation of

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measured morphometric parameters into the model geometry would better represent anatomic contributions to the predicted exchange.

A classical approach to modeling air-mucosa-capillary gas exchange was developed by Weibel and colleagues (17–19) for the lung. Their method includes a detailed, fine-structure analysis of certain morphometric parameters including diffusional length ($\tau$), which are then used to calculate the mucosal Dm. They treated the pulmonary mucosa as a continuous series of sequential segments that each contribute to Dm, and $\tau$ was measured as the harmonic mean of all pathway lengths for each cross section. A study conducted by Ars and colleagues (2) measured $\tau$ within the ME as defined by the linear distance between the air-mucosa boundary and capillary surface. Although technically simple to measure, the linear distance measurement assumes that gas exchange occurs along a linear path between blood vessel center of gravity and the air-mucosa interface and, therefore, does not account for inhomogeneities in capillary distribution and/or density.

In the present study, we simulated the diffusional fields for a simple geometric model of the ME mucosa (see Fig. 1B) and evaluated which measure of $\tau$ yields a better estimate of the oxygen diffusing capacity ($DmO_2$) for the ME. There, $DmO_2$ was calculated for different model geometries by use of the two $\tau$ measures, linear and harmonic, and the results were compared with predictions from a detailed finite element model (FEM) analysis.

**METHODS**

We quantified the effect of two $\tau$ measures on $DmO_2$, for different model geometries of the ME mucosa. In brief, one-dimensional $DmO_2$ was calculated by using each of the two $\tau$ measures (linear $\tau_L$ and harmonic $\tau_h$), and the results were compared with the “true” $DmO_2$, derived from a detailed, two-dimensional FEM analysis.

**Capillary/mucosa model geometry.** For quantitative analysis, we chose the simple, yet representative, cross-sectional geometry of the ME mucosa shown in Fig. 1B. Following Weibel and colleagues (17–19), we assume that the ME mucosa is composed of sequentially repeated cross sections throughout its extent. The exchange system consists of an elliptical capillary that is the only intramucosal gas reserve, located within a rectangular section of tissue bounded inferiorly by bone, superiorly by air, and laterally by the field of capillary influence (see Fig. 1A).

As a first approximation, the model includes only the mucosal barrier to gas diffusion and neglects intracapillary effects. However, the effect of blood resistance on oxygen transport (specifically hemoglobin interaction) is significant (10, 11), constituting 10–20% of the overall resistance (see APPENDIX) and must be included in future model descriptions of macroscopic gas transport.

For a given geometry, the model parameters define variable zones of influence for the included capillary that affect gas flux between air space and capillary. The required inputs for this capillary-mucosa system include capillary depth ($L$), defined as the distance between capillary centerline and air interface; mucosal thickness ($\delta$), defined as the distance from air-mucosa interface to bone; mucosal-air interfacial length ($S_a$), representing the effective surface area per unit depth available for gas exchange within the diffusion system; and capillary aspect [width (W) to height (H)] ratio ($A_h = W/H$). $S_a$ defines one boundary for the capillary zone of influence and consequently specifies the relative capillary density within tissue. Traditionally, capillary shape is treated as having a circular cross section, but from qualitative histological analysis of ME tissue we chose to vary capillary cross-section aspect ratio in our model (see Fig. 1A).

With the exception of $\tau$, values of the required morphometric parameters were taken from the data reported for a histological study of the ME mucosa done by Yoon and colleagues (Ref. 20; see Table 1). Yoon et al. measured ME mucosal thickness in “normal” ears ($37.5 \pm 12.5 \mu m$) and ears affected by OME ($98 \pm 63.5 \mu m$), from which we based our estimate mean ($50 \mu m$). Yoon et al. also reported capillaries per 100 $\mu m$ length tissue (a measure of capillary density within ME mucosa) as $2.00 \pm 0.72$ and $4.07 \pm 2.20$ in normal and OME ears, respectively, which is equivalent to a mean air-mucosa interface length of $50 \mu m$. Capillary depth was estimated to fall within the defined tissue section dimensions, and aspect ratio was estimated to range from 1 to 4 from qualitative ME mucosa slide observations. Also listed in the table are the physiochemical transport constants.
that outputs the DmO₂ for different model geometries. There, gas-exchange study. 

### One-dimensional conductance model

To describe gas exchange for this simple geometry, we applied a one-dimensional diffusion model that outputs the DmO₂ for different model geometries. There, gas exchange within the ME mucosa can be represented as a one-dimensional oxygen flow (Q˙O₂),

\[ Q_{O_2} = \alpha_{O_2} D_{O_2} S_a \frac{\Delta P_{O_2}}{\tau} \]  

(1)

The physiochemical parameters, \( \alpha_{O_2} \) and \( D_{O_2} \) are mean oxygen solubility and diffusivity in the mucosal tissue (see Table 1). Morphometric parameters required to represent the system geometry include \( S_a \) and \( \tau \). \( S_a \) is defined as the effective surface area for gas exchange, which is equivalent to the length of the air-tissue interface given a unit depth of tissue, and \( \tau \) is defined as the distance a gas species must travel along the diffusional path during exchange. The pressure gradient (\( \Delta P_{O_2} \)) is defined as the oxygen pressure difference between ME air space and local blood, or

\[ \Delta P_{O_2} = P_{O_2}^a - P_{O_2}^{blood} \]  

(2)

DmO₂ is then given by the lumped transport parameter,

\[ D_{mO_2} = \alpha_{O_2} D_{O_2} S_a \frac{S_a}{\tau} \]  

(3)

which represents the effective resistance of the mucosa to passive gas exchange as shown in the resulting equation:

\[ Q_{O_2} = D_{mO_2} \Delta P_{O_2} \]  

(4)

### Methods for morphometric measurement of diffusional length

A cartoon outlining the two methods of measuring \( \tau \) is presented in Fig. 1C. There, the simple linear measure \( \tau_I \) was defined as the distance from the air-mucosa interface to the capillary surface and the harmonic distance measure, and \( \tau_H \) was defined as the harmonic mean of the discrete measurements for the shortest distance between points along the air-mucosa interface and capillary surface. For the latter, \( \tau \) was treated as representing a collection of parallel diffusion pathways, and the inverse of \( \tau_H \) was approximated by summing the inverse distance measures over the surface length and dividing by the number of measures,

\[ \frac{1}{\tau_H} = \frac{1}{n} \sum_{i=1}^{n} \frac{1}{\tau_i} \]  

(5)

This calculation places greater weight on the shorter interface-capillary paths, which is expected to better represent local gas exchange.

### Results

Each of the two measures was calculated for the different model geometries, and the results were used to estimate the respective DmO₂ values for those geometries: \( \text{Dm}_o^\prime \) and \( \text{Dm}_o \).

### Finite element analysis

Earlier studies used FEM to calculate Dm for the pulmonary mucosa (13, 15). We used a similar FEM method to describe the two-dimensional ME gas-exchange system. That model utilizes the governing steady-state diffusion equation,

\[ \alpha_{O_2} D_{O_2} \nabla^2 P_{O_2} = 0 \]  

(6)

where \( \nabla^2 = (\partial^2/\partial x^2) + (\partial^2/\partial y^2) \) is the Laplacian operator and \( P_{O_2} \) is oxygen partial pressure. We assume that oxygen exchange is primarily diffusion limited in that mucosal blood perfusion does not significantly affect local tissue partial pressure. Although this assumption is supported by previous work that analyzed the contribution of convection to pulmonary gas flux (10, 11), it is included here to simplify our initial simulations and will be relaxed in later model enhancements.

Gas exchange within mucosal tissue is driven by the extant pressure gradients between local blood at the capillary surface (\( P_{O_2} = P_{O_2}^{blood} \)) and the ME air space (\( P_{O_2} = P_{O_2}^a \)) specified at the boundary condition. Because of the negligible gas diffusivity in bone, that boundary is treated as a no-flux condition:

\[ \frac{\partial P_{O_2}}{\partial x} \bigg|_{x=b} = 0 \]

Because the tissue cross section is defined as the complete zone of influence for the modeled capillary, all significant blood-tissue gas exchanges occur within the modeled region and the lateral tissue boundaries are specified as no-flux positions:

\[ \frac{\partial P_{O_2}}{\partial y} \bigg|_{y=(-)_{2}} = 0 \]

In the FEM analysis, the governing diffusive gas transport equation was solved by using the computational software package FEMLAB (version 2.3.0.145). First, for the model geometry, a wire-frame mesh network was generated that placed nodes throughout the region of interest (see Fig. 2A). Next, species partial pressure was solved at node interfaces. The mesh was refined until the computational simulation was independent of the number of elements/nodes (1,532 nodes for our baseline geometry). Total QO₂ was determined by integrating flows normal to the air-mucosa interface:

\[ Q_{O_2} = \int_s \alpha_{O_2} D_{O_2} \frac{\partial P_{O_2}}{\partial x} \bigg|_{\text{interface}} \, ds \]  

(7)

where the \( \partial P_{O_2}/\partial x \) is evaluated over the interface. The effective DmO₂ is then specified as

\[ D_{mO_2}' = \frac{Q_{O_2}}{\Delta P_{O_2}} \]  

(8)

which was accepted as the “true” value of that parameter for all model simulations.

### RESULTS

The oxygen flux fields predicted for different ME geometries by FEM analysis are shown in Fig. 2. B–D; flux vectors point in the direction of transport, and vector length is proportional to flux magnitude. The baseline cross section (Fig. 2B) contains a centrally located, circular capillary. Oxygen flux within the tissue is perpendicular to the air-mucosa interface most proximal to the capillary with very little contribution from more distal regions of the interface. The effect of changing the \( A_i \) and \( L \) on the oxygen flux field is shown in Fig. 2, C and D.
respectively. For both of these extreme conditions, oxygen flux is relatively linear and perpendicular to the air-mucosa interface.

The impact on \( \Delta m_{O_2} \) of changing the values for each geometric parameter was quantified by use of a sensitivity analysis. There, each model parameter was adjusted to \( \pm 50\% \) of the baseline value and the percent change in \( \Delta m_{O_2} \) was determined. As expected, \( \Delta m_{O_2} \) was independent of mucosal thickness (\( \Delta m_{O_2} \) \( \pm 1\% \)) but was dependent on those parameters that inherently contribute to the diffusional pathways: i.e., capillary depth (\( \Delta m_{O_2} \) \( \pm 46\% \)), capillary aspect ratio (\( \Delta m_{O_2} \) \( \pm 13\% \)), and air-mucosa interface length (\( \Delta m_{O_2} \) \( \pm 19\% \)).

The effect of varying capillary depth on \( \Delta m_{O_2} \) and \( \Delta m_{O_2} \) is shown in Fig. 3A. Differences between \( \Delta m_{O_2} \) and each of the morphometric estimates are large at small capillary depths (e.g., \( L \) of 15: \( \Delta m_{O_2} \) 76.4% difference and \( \Delta m_{O_2} \) 26.3% difference) but are less at large capillary depths (e.g., \( L \) of 65 \( \mu m \): \( \Delta m_{O_2} \) 13.4% difference and \( \Delta m_{O_2} \) 10.8% difference). This effect of capillary depth on estimate deviation is explicable by the nonuniform diffusion fronts that develop for small depths, which cause heterogeneous, proximal to distal decreases in gas flux along the air-tissue interface. In contrast, for larger capillary depths, more uniform diffusion fronts develop, allowing for more homogeneous gas flux across the entire air-mucosa interface, an assumption made in the morphometric models.

Note that for all capillary depths, the estimate provided by \( \Delta m_{O_2} \) more poorly represents the respective \( \Delta m_{O_2} \) compared with the \( \Delta m_{O_2} \) estimate, showing that the latter captures more complete information with respect to system geometry.

The effect on the three \( \Delta m_{O_2} \) estimates of varying capillary aspect ratio over the range from 1 to 4 is shown in Fig. 3B. On the basis of qualitative, histological study of ME mucosal specimens that demonstrate orientation of the capillary “long axis” along the width parameter, we chose to model this geometry by maintaining a constant height and varying capillary width. Because the \( \tau_L \) measure does not incorporate variance in capillary shape, \( \Delta m_{O_2} \) was independent of \( \Delta m_{O_2} \). Deviation between \( \Delta m_{O_2} \) and \( \Delta m_{O_2} \) was less than that between

Fig. 2. A: finite element mesh network used for detailed analysis of gas flux, and the corresponding oxygen diffusion fields predicted by finite element model analysis for a basal condition (B), increased capillary aspect ratio (C), and larger capillary depth (D).

Fig. 3. Predicted mucosal diffusion capacitance (\( \Delta m_{O_2} \)) as a function of capillary depth (\( L \); A), capillary aspect ratio (\( A_r \); B), and tissue-air interface length (\( S_a \); C) for the 3 estimation methods (see text).
DmO₂ and DmL₂ over all Aᵣ. This effect is explicable by the heterogeneous diffusion fronts present for circular capillaries where flux contributions decrease progressively from more distal regions of the air-mucosa interface, a property more accurately captured by τᵣ. However, our results show that Aᵣ was not a dominant factor in DmO₂ classification, with DmO₂ prediction only varying ~10% from a 400% increase in Aᵣ. This result allows us to conclude that Aᵣ is not a geometric characteristic important to gas exchange and gives us confidence that artifacts in capillary shape resulting from oblique slicing would not introduce significant errors.

The effect of varying tissue-air interface length on the three estimates of DmO₂ is shown in Fig. 3C. Lesser deviations between DmO₂, and both DmO₂ and DmL₂, are evident at smaller lengths (S_a of 25 µm: DmO₂ 13.36% difference and DmL₂ 8.32% difference) compared with the more pronounced deviations at larger lengths (S_a of 75: DmO₂ 73.4% difference and DmL₂ 32.9% difference). Larger air-mucosa interfaces (per capillary) reflect lower capillary density, whereas smaller interfaces represent more uniform capillary distributions throughout the mucosa. This relationship respectively mimics the effects of the high and low Aᵣ on flux fields as discussed above. As with the other simulated geometries, better agreement between the derived DmO₂ estimates and DmL₂ is achieved by using the τᵣ measure.

**DISCUSSION**

A fundamental, mathematical description of transmucosal gas exchange for the normal and diseased ME can be used to explain the mechanism underlying the development and persistence of otitis media with effusion, as well as to suggest options for the targeted treatment of that disease (5). Compartmental exchange models are not mechanistically determinant and therefore cannot be used for those purposes. This limitation can be avoided by using morphometric models that include fine structure details of parameters known to influence gas exchange between the ME air space and mucosal capillary (7).

In modeling gas exchange for the lung, the required morphometric parameters for accurate representation of physiology included tissue volume, capillary distribution, and the surface areas for the exchange unit (17–19). That approach requires first determining the effective τ for a given geometry, which is then used to generate the diffusional properties for specified mucosal geometries (17–19). Here, we used a modification of that approach to model transmucosal gas exchange for the ME (2).

When used as morphometric model inputs, measurement of all relevant geometric parameters for all ME regions and under all mucosal conditions (e.g., age, disease state, etc.) is expected to yield results that accurately predict ME transmucosal gas exchange for the normal and diseased mucosa. However, such an approach is not technically feasible. Consequently, a first priority for model development is the definition of a measurement subset that captures the information most important to system dynamics as reflected by predictive accuracy. One parameter known to be a member of that subset is τ, which represents the effective length of the diffusion pathway between air-mucosa interface and capillary. In this study, we compared two relatively easy techniques for measuring τ with respect to their ability to generate DmO₂ sets for different ME mucosal geometries that are consistent with the respective set generated using a more complex FEM approach where τ is not an input parameter (2, 13–15, 17, 19). The results showed that the τ defined by the harmonic mean distance better represents the DmO₂ for the FEM analysis. This predictive improvement is attributable to the fact that, unlike the linear measure, the harmonic mean measure incorporates information related to capillary shape and density.

Nonetheless, neither one-dimensional, morphometric model accurately represented the DmO₂ set predicted by the FEM analysis. The morphometric estimates predicted DmO₂ appropriately in some instances (large L, large Aᵣ, and small S_a) but erroneously in others (small L, small Aᵣ, and large S_a). These simple models overestimated the DmO₂ (positive bias) and the magnitude of the error varied with extant conditions (nonlinear bias). This exposes limitations of even our better one-dimensional model for ME transmucosal gas exchange and shows that results from such simulations cannot be used to accurately predict the continuum of change in gas-exchange behavior from the normal to pathological mucosa. We question the applicability of a morphometric approach to estimating geometric parameters within this specific exchange system: the ME mucoa.

Weibel’s successful formulation of pulmonary gas exchange using a morphometric model led us to a similar approach for describing ME transmucosal gas exchange (17–19). However, as evidenced by the comparative simulations reported here, we adopted a cautious, stepwise approach that first explored the adequacy of the morphometric model to accurately represent system behavior. There, we recognized that there are significant differences in the fine structure of the exchange system for the lung and ME. For example, alveolar walls are thin tissue structures, embedded with capillaries, and symmetrically bounded by air space. Gas exchange within this geometry can be described using symmetry, with capillary surfaces proximal to air interface boundaries specified as the “active” sites for air-space-mucosa-capillary gas exchange.

However, this simplifying assumption fails for the ME mucosal geometry where bone opposes the basal mucosal surface allowing the entire capillary surface to participate in mucosa-blood exchange with a single air interface (see Fig. 2B). Also, the flux fields generated by FEM analysis document curvilinear diffusion paths, an effect not reproduced in the morphometric models, which assume linear species transport and contributions from the total available surface area. A similar discrepancy between the results for red blood cell diffusing capacity in pulmonary capillaries generated by morphometric models and FEM analysis was noted by Hsia and colleagues (14, 15). There, morphometric models contained “fundamental oversimplifications,” unable to account for factors found important to gas exchange. These and other differ-

**Table 2. Analysis of membrane and intracapillary component contribution to total diffusing capacity**

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<th>Estimate Value</th>
<th>DLO₂ ( \times 10^{14} )</th>
<th>DLO₂ ( \times 10^{14} )</th>
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<th>Membrane % Contribution</th>
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*Source: J Appl Physiol • VOL 98 • JANUARY 2005 • www.jap.org*
ences in pulmonary and ME mucosal geometry may explain the failure of the morphometric models developed for the lung to accurately represent the $D_{mO_2}$ for the ME mucosa.

**APPENDIX**

**Approximation of Intracapillary Oxygen Diffusing Capacity**

Inclusion of intracapillary gas transport within calculation of the total diffusing capacity is defined as

$$\frac{1}{D_{LO2}} = \frac{1}{D_{mO2}} + \frac{1}{\Theta V_c},$$

(9)

where $D_{LO2}$ is the total oxygen diffusing capacity, $D_{mO2}$ is the membrane component, $\Theta$ is the specific oxygen resistance of transport from the red blood cell membrane to the hemoglobin molecule in whole blood (per time), and $V_c$ is the total capillary volume. From this, we approximated the percentage contribution of membrane and intracapillary components to total diffusing capacity for our model baseline geometry. We calculated the membrane component of oxygen diffusing capacity ($D_{mO2} = 6.95 \times 10^{-14}$ mol oxygen s$^{-1}$ cm$^{-1}$ Torr$^{-1}$) from values in Table 1. For the reactive component, we multiplied the baseline geometry capillary volume ($V_c = 4.85 \times 10^{-7}$ cm$^3$) by published estimates for oxygen uptake rate ($\Theta$) (16). Table 2 shows the percent resistance attributable to each component of diffusing capacity for each $\Theta$ estimate. This brief analysis shows that the membrane component is the dominant controlling factor to total diffusing capacity, but intracapillary resistance remains an important aspect by contributing $\sim 10$–20%.

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