

## Section 4: Mini-Symposium-1: Endolymph Regulation and Mechanism of Hydrops

### **Low Frequency Pressure Changes May Participate in Endolymph Volume Regulation**

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Endolymph is truly unique among the extracellular body fluids, in more ways than we have previously appreciated. A number of established concepts associated with other fluids, such as the concept of “secretion” (i.e. the process of generating new fluid in volume), simply do not apply to endolymph. The high metabolic costs of endolymph generation have resulted in highly efficient homeostatic processes that avoid the need to discard fluid in volume. Instead, the ionic composition of endolymph is largely maintained by local ion transport processes, in which the major ions are actively recycled between perilymph and endolymph.<sup>1</sup> This process of ion recycling occurs with negligible associated volume flow, and occurs in the absence of any physiologically-significant longitudinal endolymph flow in the cochlea.<sup>2</sup>

#### **Endolymph Flow**

Under some conditions, the near-stationary, normal state of the endolymph can be disturbed and longitudinal flows can be induced. Injections into the endolymphatic space result in longitudinal volume flow towards the base of the cochlea.<sup>3</sup> The presence of injection-induced flow towards the sac is in complete agreement with the data from early experimental studies<sup>4</sup>, but we now know that this observed flow does not represent the normal state, but is caused by the injection procedure itself. Longitudinal flow during endolymphatic injections appears to result from the passive mechanics of the boundary membranes of the endolymphatic system, in which the saccule provides a more mechanically-compliant compartment.<sup>5</sup> The pressure changes observed during injections are consistent with endolymph flowing through a small duct (the ductus reuniens) into a more compliant compartment (the saccule). In these pressure measurement studies it was also found that initial volume manipulations occurred without detectable hydrostatic pressure increase in endolymph, consistent with the membranous boundaries of the endolymphatic compartments initially being highly compliant. Hydrostatic pressure changes during small disturbances of endolymphatic volume are therefore expected to be extremely small.

Endolymph volume flows are not always basally directed. Experimental manipulations that decrease endolymph volume in the cochlea, such as by endolymph withdrawal or by osmotic dehydration, result in apically directed flow. This is again determined by the compliance characteristics of the endolymphatic boundaries in which the saccule appears to collapse more readily during volume decreases. Thus, the role of flow, and by inference, the role of the endolymphatic sac, in volume regulation appears to be in either direction, as dictated by mechanical requirements and as required to stabilize endolymph volume.

#### **The Role of the Endolymphatic Sac**

The endolymphatic sac is lined with an uneven epithelium, with characteristic crypts and folds. Present in the tissues are a variety of ion transporters<sup>6,7</sup> and aquaporins<sup>8,9</sup>. There is general agreement that the structure is consistent with fluid and ion transport being a primary function of the sac. The endolymph in the lumen of the sac is characterized as having a low  $K^+$  content (10 – 15 mM), a higher  $Na^+$  content (100 – 140 mM) relative to the rest of the endolymphatic system, and a resting potential of 6-20 mV.

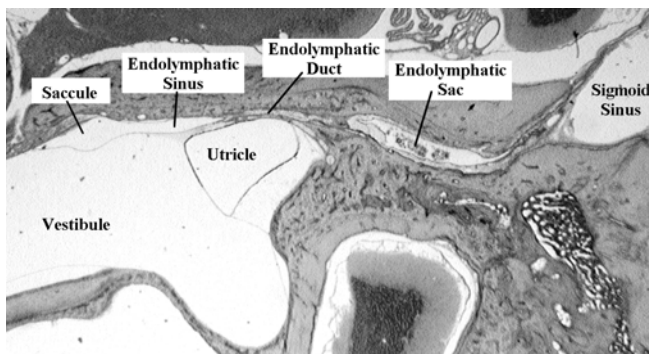
Physiologically, the sac has been shown to be highly sensitive to endolymph volume manipulations.<sup>10</sup> When endolymph volume was increased, luminal  $K^+$  increased and  $Na^+$  concentration decreased. In contrast, when endolymph volume was decreased, luminal  $K^+$  decreased and  $Na^+$  increased. These oppositely directed ionic changes are interpreted as demonstrating that the sac has a bi-directional response, being capable of either secretion or resorption of endolymph under different conditions. In the normal state the sac appears to be delicately balanced between these two extreme states, and may have little influence on fluid status.

Morphologic observations support the view that the sac is balanced between two distinct functional states. In the normal sac, a stainable “homogenous substance” is seen filling the distal regions of the lumen. Following endolymph volume increases, the homogenous substance in the lumen disappears and the dark cells in the epithelium appear to be activated, in some cases covering the apical surfaces of the light cells in a manner described a “veiling.”<sup>11</sup> In contrast, with reductions in endolymph volume, by osmotic dehydration or endolymph withdrawal, the luminal substance becomes darker and is present throughout the lumen of the sac. In addition, the light cells become enlarged and activated. The observation that two distinct cell types appear to be activated under different conditions further supports the view that the sac performs two distinct functions, specifically the resorption of endolymph under conditions of volume excess, and the generation of endolymph volume under conditions of volume insufficiency.

#### **Detection of Abnormal Endolymph Volume States**

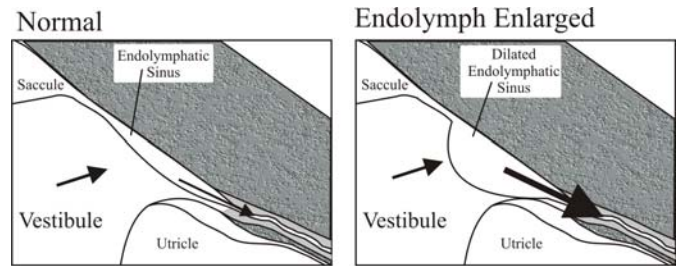
While these prior studies have shown that the sac responds actively to endolymph volume increases or decreases, the mechanism of the sac’s response, and exactly how it is triggered, has received little attention. It is assumed that when endolymph volume is enlarged, the sac resorbs endolymph, with associated physiological changes as described above. An important question however, is how is this process controlled? What causes the sac to stop when resorption is no longer required and how is the activity of the sac linked to

endolymph volume changes? The key element is how the physiologic function of the sac is controlled in a manner that is sensitive to endolymph volume status. The detection of volume change requires some form of mechanically-sensitive detector (sensitive to endolymph volume changes), yet no cells in the endolymphatic sac appear to be specialized as mechanoreceptors. The required pressure sensitivity of the detector must be high, as we anticipate the hydrostatic pressures associated with small volume disturbances are extremely small.<sup>5</sup> Indeed, a major difficulty is whether the sac itself could act as a mechanically-sensitive structure and whether could it detect a minuscule endolymph pressure increase in the presence of background pressure fluctuations. The location of the sac is not conducive to sensitive mechanoreception, since it is directly influenced by both CSF pressure fluctuations and the vascular pulsations of the sigmoid sinus, which forms one wall of the structure. Pressure measurements within the endolymphatic sac have been found to be extremely noisy<sup>12</sup>, and substantially greater than the typical pressure fluctuations observed in the perilymphatic spaces of the inner ear. Thus, the possibility that the tissues of the endolymphatic sac could be sensitive to a minuscule endolymph overpressure with respect to perilymph appears unlikely.



**Figure 1** Section through the guinea pig inner ear showing the relationship between the endolymphatic sinus, the endolymphatic duct and the endolymphatic sac.

As an alternative explanation, we propose that detection of endolymph volume status does not occur within the endolymphatic sac itself, but instead is performed at the level of the endolymphatic sinus, the small membranous bulb located where the endolymphatic duct enters the vestibule (Figure 1). Measurements in the sac have shown that when the pressure of perilymph of the vestibule is increased, communication with the sac is occluded, presumably as the membranous wall of the sinus closes the duct.<sup>12</sup> However, when repeated low-frequency pressure pulses were applied to the vestibule an increase in luminal  $K^+$  concentration was seen in the sac, suggesting that the sinus was allowing small pulses of endolymph to be driven into the sac.<sup>12</sup> These data suggest that endolymph movements driven by fluctuating pressures in the vestibule could play a central role in endolymph volume regulation. The proposed role the endolymphatic sinus plays in regulating endolymph flow into the sac is schematized in Figure 2. A major source of positive pressure fluctuations in the vestibule is the contractions of the middle ear muscles, most notably contractions of the tensor tympani, that occur during swallowing. The resulting stapes movements produce longitudinal endolymph movements in the cochlea and large endocochlear potential changes associated with the sustained positive pressure pulse that lasts approximately 0.5s.<sup>13</sup>

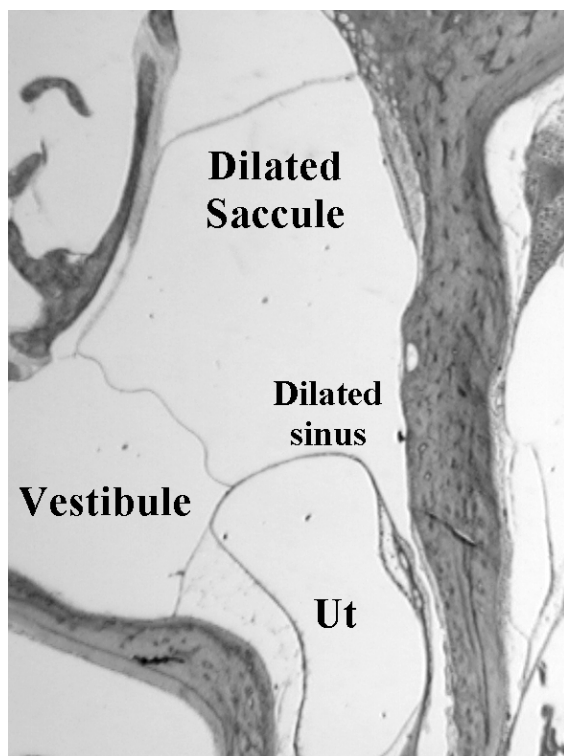


**Figure 2** Schematic of how the endolymphatic sinus detects and regulates endolymph volume status. When endolymph volume is normal (left), pressure elevations in the vestibule (black arrow) produce only small endolymph movements into the sac before the sinus membrane occludes the duct. In contrast, when the endolymphatic sinus is dilated (right), pressure elevations in the vestibule result in a larger volume being forced into the sac before the duct is occluded. The increase in volume delivered to the sac with dilation of the endolymphatic sinus will act to counteract the volume increase, acting to stabilize endolymph volume within a specific range.

If the membrane comprising the endolymphatic sinus is highly compliant, then the slightest overpressure of the endolymphatic system would result in greater distension of the sinus. In this state, positive pressures applied to the vestibule would drive greater amounts of endolymph into the endolymphatic sac before the flow was occluded by the sinus membrane. This process would thereby act to compensate for the volume increase. The advantage of such a system is that it uses the normal pressure fluctuations between the labyrinth and the cranium to drive fluid to or from the sac, while flow control from the labyrinth to the sac depends exquisitely on the small overpressure of endolymph with respect to the surrounding perilymph that determines the degree of dilation of the sinus.

The sources of pressure fluctuations in the ear are numerous, but the important factors that influence flow through the endolymphatic duct are likely to be those where the labyrinth and the cranium show differences in pressure, thereby creating a pressure gradient across the duct. As the fluctuations of CSF pressure associated with respiration, heartbeat, postural movements, coughing, sneezing, etc, are also transmitted to the labyrinth via the cochlear aqueduct, these sources are unlikely to drive endolymph flow through the duct. It is possible that if the cochlear aqueduct is occluded, then significant pressure differentials between the labyrinth and cranium could occur. Of likely greater importance, however, are the sources of low frequency pressure changes from the middle ear that directly influence labyrinthine pressure so that pressure differentials between the labyrinth and CSF will be generated. This includes externally applied low frequency sound, middle ear pressure changes, pressures generated by middle ear muscle contractions and inertial pressures generated by head movements. Due to the attenuation characteristics of the middle ear for low frequency sound, the major source of substantial pressure changes in the ear is likely to be from middle ear muscle contractions. It remains uncertain whether dysfunction in the middle ear, either of the muscles or in the mobility of the stapes, could give rise to endolymphatic disturbances. It is quite possible that other sources of pressure fluctuation, such as those from head movements, may be sufficient for the system to function normally.

While the potential role of the endolymphatic sinus in controlling fluid movements into the endolymphatic sac is an interesting concept, there appears to be an inherent instability in such a system. If endolymph volume excess ever exceeds the capacity of the sac to resorb it then the endolymphatic sinus membrane will become dilated to the point where it can no longer function as a flow-limiting valve. Figure 3 shows the extreme case of dilation of the endolymphatic sinus in an animal with surgically-induced hydrops, in this case induced by surgical ablation of the endolymphatic sac. The membranous wall of the sinus is displaced to an extent that it is in contact with the wall of the utricle. In the hypothetical situation where the endolymph space is hydroptic, and the sac is still intact, positive pressures in the labyrinth should still cause endolymph to enter the endolymphatic duct and sac. It remains uncertain whether the sinus could eventually recover its normal anatomy and function following such a period of dilation.



The possible dependence of endolymph volume regulation on low frequency pressure fluctuations in the ear appears consistent with the use of increased levels of low frequency stimulation as a therapy for endolymphatic hydrops. This is the present basis of the Meniett device marketed by Medtronic/Xomed. On the basis of our observations in experimental animals, the general principles of the device appear to be supported, although the specific design of the pressure delivery system cannot yet be evaluated.

In summary, we propose that the “detector” of abnormal endolymph volume states is not the endolymphatic sac, but is instead the membranous endolymphatic sinus. By limiting endolymph flow into the duct when endolymph volume is low, and by allowing more flow into the duct when endolymph volume is high, this structure may control and regulate endolymph volume status.

## Acknowledgements

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