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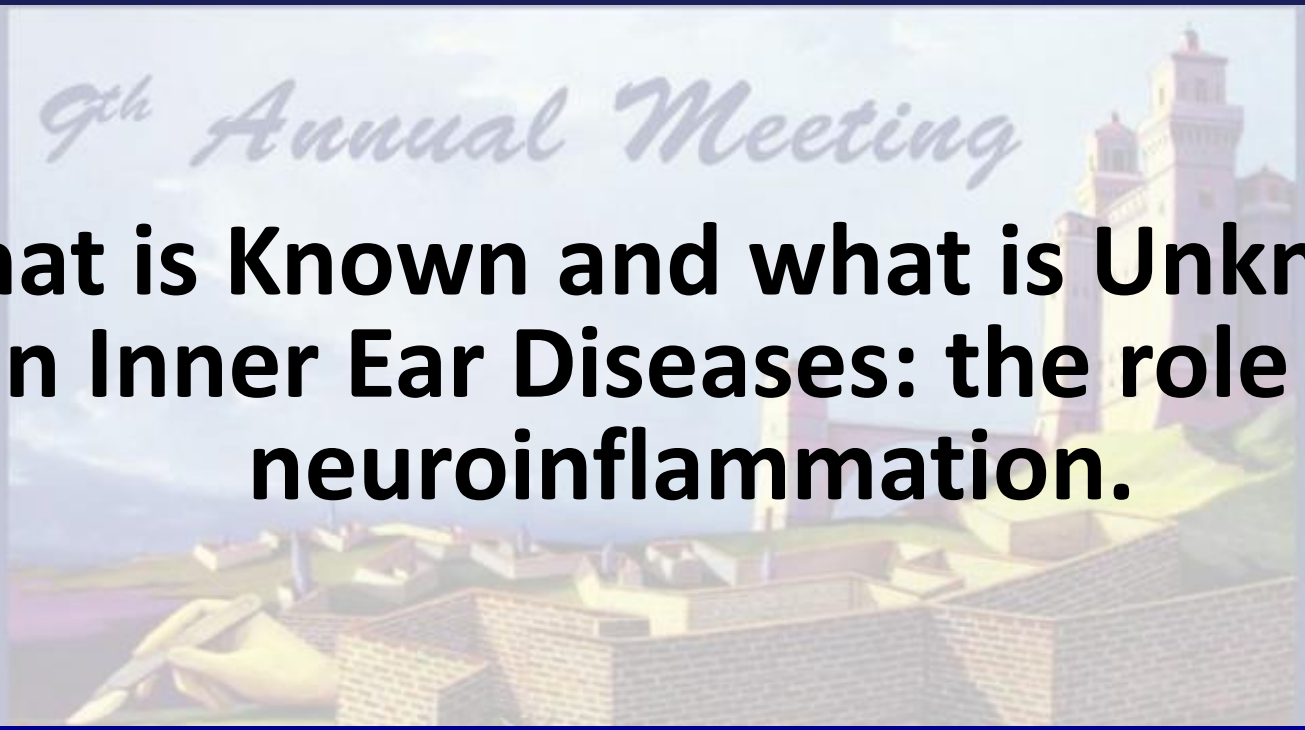
International Society for Neurovascular Disease

INTERNATIONAL SOCIETY FOR NEUROVASCULAR DISEASE

Ferrara, May 30-31, 2019, Italy

AULA MAGNA, S. ANNA UNIVERSITY-HOSPITAL, CONA VIA ALDO MORO 8

Meeting President Prof. Paolo Zamboni, University of Ferrara



What is Known and what is Unknown in Inner Ear Diseases: the role of neuroinflammation.

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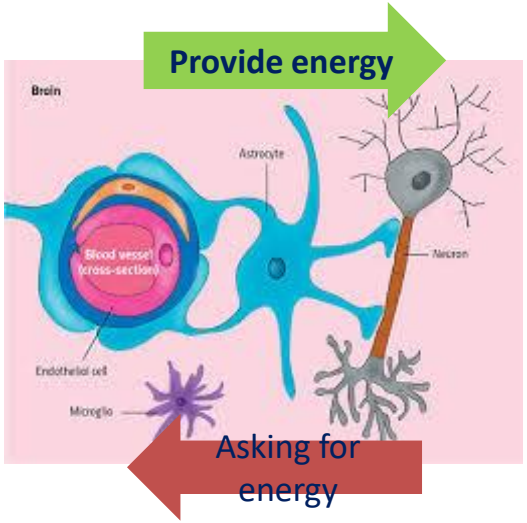
The NeuroVascular Unit - NVU

- The concept of **neurovascular unity** has been present for a long time simply defining the coupling between neuronal activity, requiring energy, and blood flow, energy dispenser.

- In 2002 during the first Stroke Progress Review Group meeting this concept has been revised acquiring more importance.

- The NVU could be considered as the result of the continuous interaction between different types of cells (glia and neurons), cerebral blood vessels, extracellular matrix in order to create an highly functioning structure whose activity would be crucial for a correct brain function, in development and learning



Neuron
Review

The Neurovascular Unit Coming of Age: A Journey through Neurovascular Coupling in Health and Disease

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http://dx.doi.org/10.1016/j.neuron.2017.07.030

- From the initial description the concept has evolved towards ‘extended NVU’ that includes other cell types, **pericytes and microglia**, and specialized cellular compartments such as **endothelial glycocalyx**.
- if on one hand a suitable functioning of the NVU allows a good homeostasis and neuronal welfare, its dysfunction can lead to aging as well as potential pathologies.
- A dysfunction of the NVU can be due to **primary vascular injuries** (arterial hypertension, diabetes, haematic hyperviscosity) or **primary neuronal injuries**. In both cases we will obtain a dysfunction of the NVU, mostly due to **inflammation**.
- similar interactions occur in barriers such as the **blood-brain barrier**. Here the NVU has a function of signaling, of mediation of chemical, enzymatic, and pressure signals useful to modulate the vascular response.

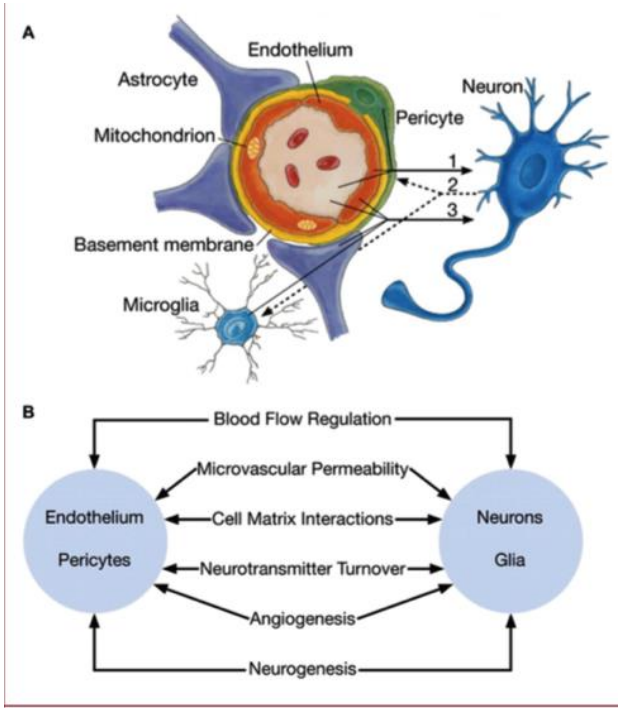

FIGURE 1. A, Schematic of the neurovascular unit. In neuronal disorders that have a primary vascular origin, circulating neurotoxins cross the blood–brain barrier to reach their targets, or proinflammatory signals from vascular cells or reduced capillary blood flow disrupt normal synaptic transmission and trigger neuronal injury (arrow 1). Microglia sense signals from neurons (arrow 2). Activated endothelium, microglia, and astrocytes signal back to neurons, which in most cases aggravate the injury (arrow 3). In primary neuronal disorders, signals from neurons are sent to vascular cells and microglia (arrow 2), which activate the vasculoglial unit and contribute to progression of injury (arrow 3). B, Coordinated regulation of normal neurovascular functions depends on vascular cells (endothelium and pericytes), neurons, and astrocytes. Reprinted Neuron 57(2), Zlokovic et al.[3] The blood-brain barrier in health and chronic neurodegenerative disorders, pp 178–201, 2008, with permission from Elsevier.

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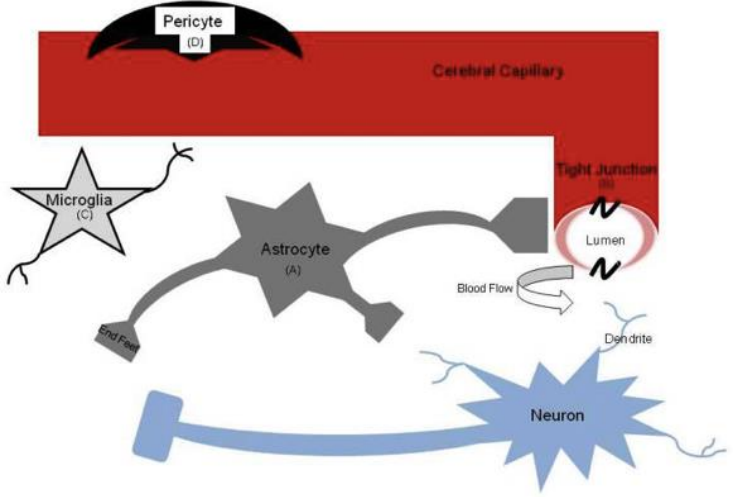


In CNS NEURON FUNCTION DEPENDS UPON A HOMEOSTATIC MICROENVIRONMENT, WHICH RESULTS FROM NVU CELL-CELL INTERACTIONS

(A) Astrocytes interpret neuron signaling and modify release of factors in order to help maintain neuron metabolic needs. Astrocyte end feet have close contact with the cerebral endothelium, which helps to regulate blood flow and tight junction integrity.

(B) Tight junctions provide an epithelial-like quality to the BBB, **creating a physical and electrical barrier to prevent paracellular molecular passage.**

(C) Pericytes maintain basal lamina structure and may regulate blood flow. Evidence suggests the basal lamina is a point of contact for NVU intracellular communications. Proper structure is needed for sending and responding to cell-cell communications.

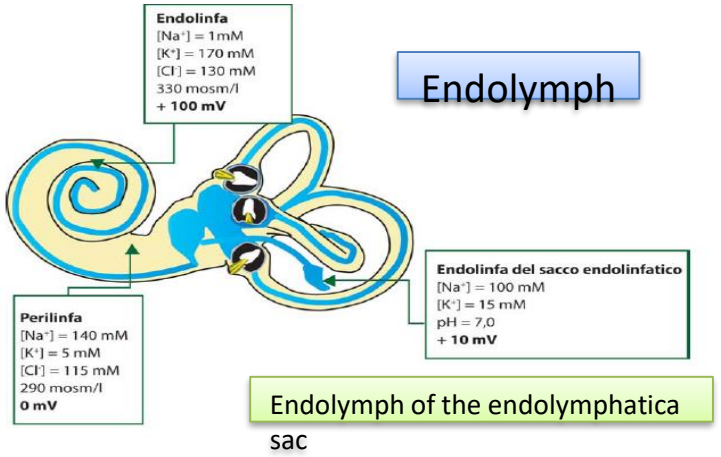
(D) Microglia are cerebral monocytes that possess a stellate shape under physiological conditions. Physiological function of microglia within the NVU is not well defined.

- **In pathological conditions, Astrocytes interpret distress signals, become activated so they release inflammatory cytokines and enzyme (e.g. MMP-9) leading to tight junction proteins degradation,**
- **Dysfunction or lack of pericytes leads to basal lamina thickening, which dysregulates NVU cell signaling and hemodynamics of cerebral blood flow.**

- A structure similar to NVU is present in the inner ear, the so-called **blood labyrinthine barrier (BLB)**.

- BLB refers to the barrier between the vasculature and the inner ear fluids, endolymph or perilymph. The BLB is critical for the maintenance of the inner ear fluid ionic homeostasis and for the prevention of the entry of deleterious substances into the inner ear

  - endothelial cells of the labyrinthine microcirculation joined by **tight junctions** that, together with the proteins of the Reissner membrane and the basal and marginal cells of the vascular stria, contribute to maintain as separate the compartment of the inner ear and to regulate the movements of the ions. This condition is necessary to maintain endolabyrinthine potentials and so the functioning of the hair cells and therefore of the audiovestibular function.

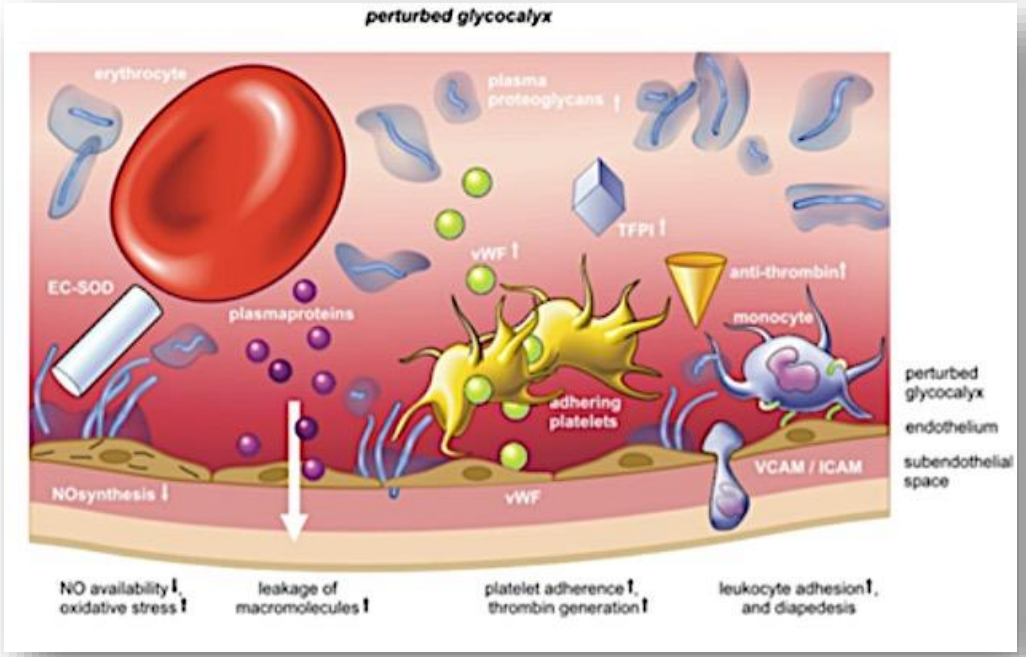


The common denominator of the two barriers so far considered is the **endothelium** that covers the luminal surface of the vessels.

The endothelium in physiological conditions has an additional coating that represents the true interface with the bloodstream, the **glycocalyx.**

The loss of the glycocalyx, due to haemodynamic, thrombogenic or metabolic causes, exposes the endothelial cells to the blood stream and determines the onset **of inflammatory phenomena** affecting the vessel wall with platelet activation, release of thrombogenic factors, reduction of fibrinolytic activity, according to a damage based on endothelial inflammation.

Hyperlipemia, blood hyperviscosity, diabetes, and arterial hypertension contribute to glycocalyx damage

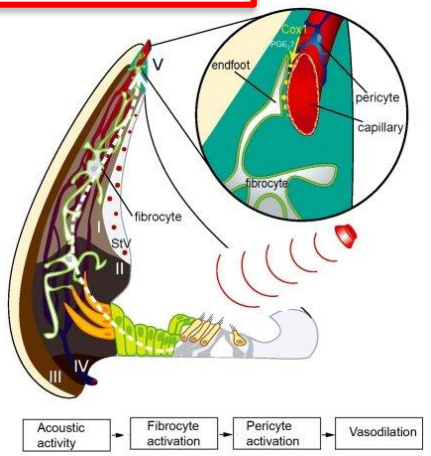


Cochlear Capillary Pericytes

Martin Canis and Mattis Bertlich

- Formation of the intrastrial blood-fluid barrier—Pericytes monitor the ion, fluid, and nutrient household and aid in the homeostasis thereof.
- Regulation of cochlear blood flow—By contraction on relaxation, pericytes contribute to the regulation of cochlear blood flow, a paramount function parameter of the cochlea.
- Immune response—Pericytes actually contribute to the immune response in inflammation of the cochlea.

Due to these central roles in the physiology of the cochlea, pericytes actually play a major role in numerous cochlear pathologies, including, but not limited to, sudden sensorineural hearing loss, acoustic trauma, and inflammation of the cochlea.



Menière's disease

- ✓ High level of anti-phospholipid Ig
  - ✓ (anticardiolipin, AutoAC anti-β2 glycoprotein; Lupus anticoagulant)
- ✓ Primary or associated with other autoimmune diseases
- ✓ Associated with thrombotic syndromes
  - ✓ For activation of coagulation cascade
  - ✓ Microemboli in the labyrinthine circulation
  - ✓ Need for treatment with anticoagulants
  - ✓ No ASA or thesimilar drugs are effective
  - ✓ Treatment in case of thrombotic phenomena

Conclusion: In general, the results of this study do not support the hypothesis that immune or infectious pathologies are involved in the pathogenesis of unilateral Ménière's disease. In particular, Lyme disease does not seem to cause labyrinthine disease. However, the potential role of the thrombogenic antiphospholipid antibodies must be further investigated. Patients with bilateral Ménière's disease may be more likely to have a systemic autoimmune process. **Key Words:** Autoimmune—

Otology & Neurotology
24:617–621 © 2002, Otology & Neurotology, Inc.

Immunologic and Serologic Testing in Patients with Ménière's Disease

*Michael J. Ruckenstein, *Anna Prasthoffer, *Douglas C. Bigelow, †Joan M. Von Feldt, and †Sharon L. Kolasinski

TABLE 1. *Serologic and immunologic testing*

Test	Major associated diseases
Complete blood count	
Electrolytes, BUN, creatinine	
Urine analysis	
Antinuclear antibodies	
Peripheral	SLE
Homogeneous	SLE
Speckled	SLE, Sjögren disease, mixed connective disease, scleroderma, polymyositis, CREST syndrome, rheumatoid arthritis
Nucleolar	Scleroderma, polymyositis
Anti-double-stranded DNA	SLE
Anti-Sjögren syndrome A and B	Sjögren disease
Rheumatoid factor	Rheumatoid arthritis
Complement levels	Maybe decreased in SLE, Sjögren disease, and vasculitides
C3	
C4	
Antiphospholipid antibody screen	Antiphospholipid antibody syndromes
Western blot for heat shock protein 70	Steroid responsive (autoimmune) inner ear disease
MHA-TP	Secondary/tertiary syphilis
Lyme titers	Lyme disease

BUN, blood urea nitrogen; SLE, systemic lupus erythematosis; CREST, calcinosis cutis, Raynaud phenomenon, esophageal motility disorder, sclerodactyly, and telangiectasia; MHA-TP, microhemagglutination test for *Treponema pallidum*.

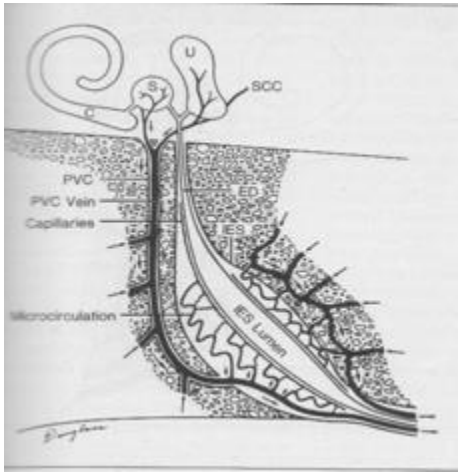
Menière's disease

Arch Otolaryngol. 1982 Sep;108(9):544-9.

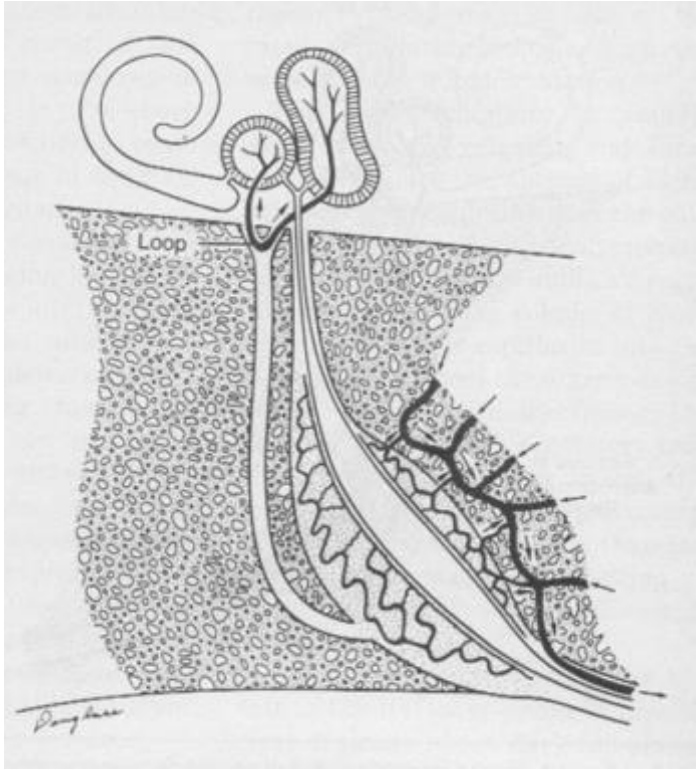
Vascular mechanisms in Meniere's disease. Theoretical considerations.

Gussen R.

1982 Gussen, had assumed that the hydrops was the consequence of an increase in venous pressure at the labyrinth level, an idea by histopathological studies



- The inferior cochlear vein drains from the cochlea and from the vestibular receptor areas
- The vein of the vestibular aqueduct (or vein of the paravestibular canaliculus, PCV) drains the areas adjacent to the receptors including the area of dark cells (areas involved in the mechanism of production and transport of OI liquids) and receives tributaries from the regions of the ES.
- In 25% of the subjects the PCV receives vestibular veins normally tributary to the cochlear inf
- In this case an increase of venous pressure can occur leading to an insufficient endolymphatic drainage with EH
- The congenital absence of the PCV vein can induce EH



Menière's disease

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- ✓ Relationships between PCV and the vascular system of the ES
- ✓ MD temporal bone → Perisaccular fibrosis with microcirculation alteration. If PVC drains no EH; otherwise EH
- ✓ Fibrosis can result from a persistent edema of the perisaccular region induced by insufficient venous drainage
- ✓ In the perisaccular area there is a real microcirculatory system that controls the volume of blood drained from the bag region towards the PCV vein
- ✓ An increase of pressure in the PCV vein leads to reduced drainage in areas that produce endolymph and this can induce EH.

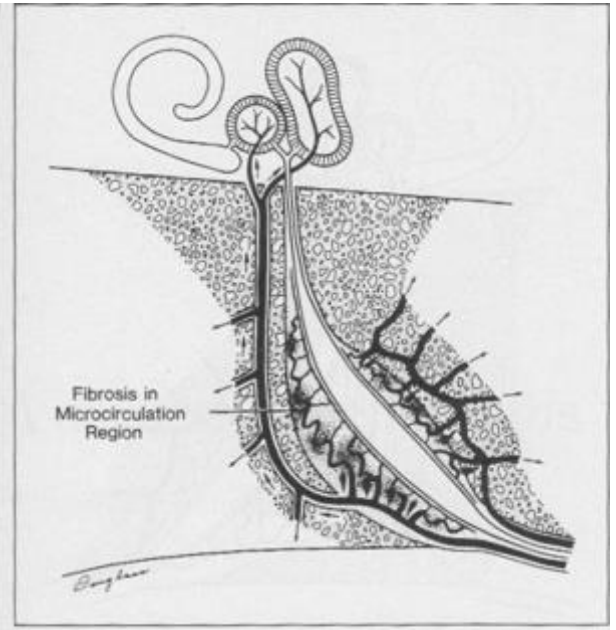


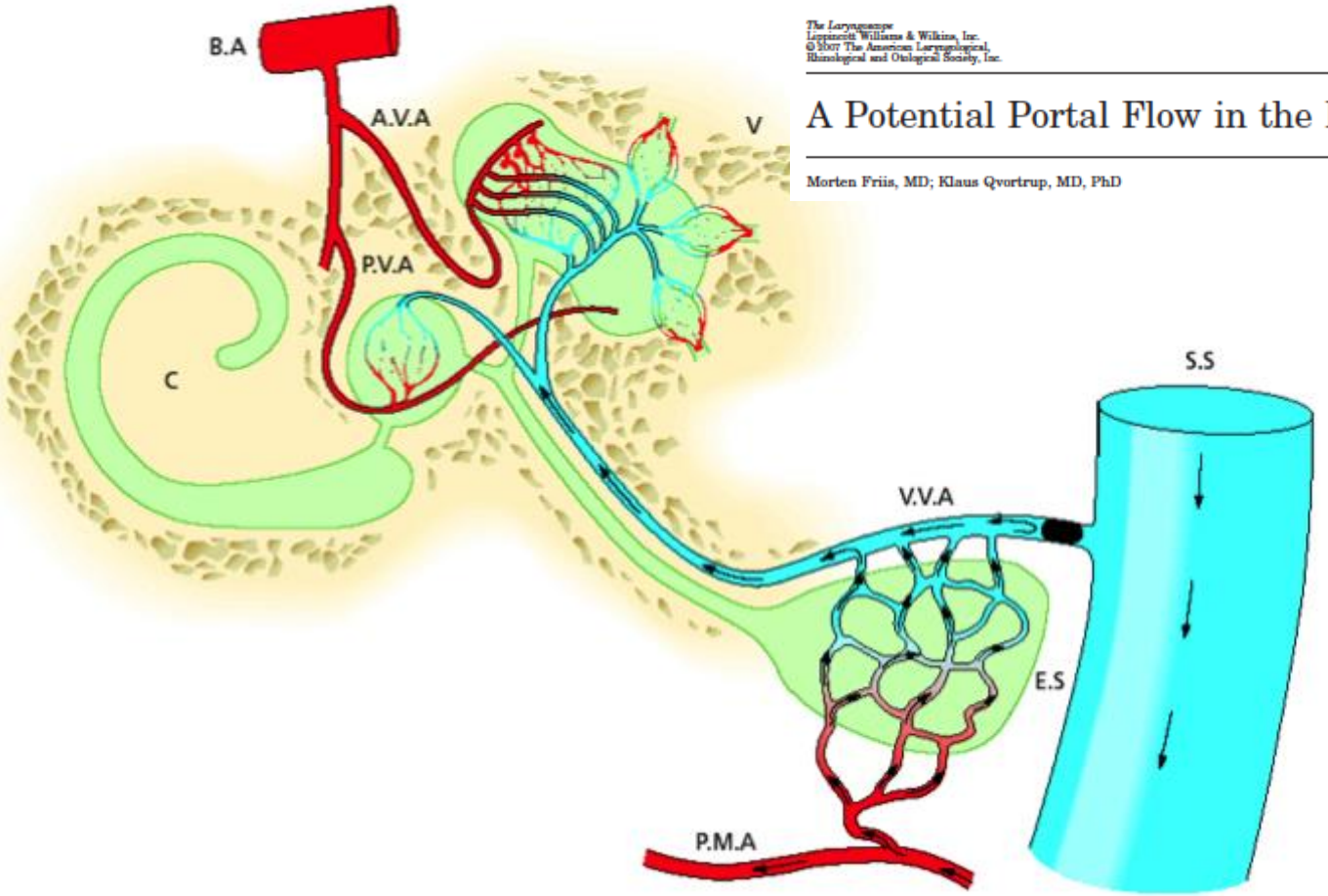
Fig 3.—Top left, Altered microcirculation of intermediate endolymphatic sac associated with fibrosis, with increased venous BP in vein of paravestibular canaliculus and other veins, denoted by reversal of arrows that also denotes possible collateral routes of venous drainage. Hydrops is present.

- **An alteration of venous drainage of the vestibular organs via the paravestibular canaliculus (PVC) vein is fundamental to inner ear fluid mechanisms.**
- **With increased venous pressure, insufficient drainage may result in a damage of BLB inducing endolymphatic hydrops, unless collateral veins develop.**

Menière's disease

A distal obstruction (thrombosis, perisaccular fibrosis, ES hypertrophy) of the VVA could lead to a reversal of the flow towards the inner ear, leading to a portal-type circulation in the inner ear through the A-V anastomoses.

This could lead to an alteration of endolymphatic production and therefore EH



The Laryngoscope
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A Potential Portal Flow in the Inner Ear

Morten Friis, MD; Klaus Qvortrup, MD, PhD

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Meeting President Prof. Paolo Zamboni, University of Ferrara

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- A dysfunction of the NVU, primarily due to neuronal or vascular problems, can cause aging or pathology
- An abnormalities of inner ear blood flow (either venous or arterial) could lead to an endothelial dysfunction causing an inflammatory damage with deterioration of the BLB and consequent inner ear pathology such as endolymphatic hydrops.
- In this process a crucial role is represented by hyperactivity and over-expression of MMPs (MMP-2 and MMP-9).

What is Known and what is Unknown in Inner Ear Diseases: the role of neuroinflammation.

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