

Cerebrospinal Fluid Transport: a Lymphatic Perspective

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The textbook view that projections of the arachnoid membrane into the cranial venous sinuses represent the primary cerebrospinal fluid (CSF) absorption sites seems incompatible with many clinical and experimental observations. On balance, there is more quantitative evidence suggesting a function for extracranial lymphatic vessels than exists to support a role for arachnoid villi and granulations in CSF transport.

In most tissues, extracellular fluid is formed by filtration. The force favoring filtration is the hydrostatic pressure in the capillary. An opposing force is provided by the colloid osmotic pressure of the plasma proteins. Usually, the forces across the capillary favor filtration, and the interstitial fluid with its protein and other solutes is absorbed by the lymphatic system and returned to the plasma. The brain is unique in that filtration from the vasculature is very low due to the blood-brain barrier. Additionally, lymphatic vessels do not exist within the parenchyma of the central nervous system.

The extracellular fluid compartment of the brain can be divided into two components, cerebrospinal fluid (CSF) and parenchymal interstitial fluid (10). CSF is produced in the human brain by four choroid plexi located within the ventricular system. The CSF flows through the ventricles into the subarachnoid space via the foramina of Luschka and of Magendie and circulates over the outer surfaces of the brain and spinal cord. Parenchymal interstitial fluid is actively secreted by the capillary endothelial cells. Interstitial fluid moves from its formation at the capillary-glia complex through the perivascular and subependymal regions into the ventricular system and subarachnoid space, where it mixes with the CSF (6).

The textbook view of CSF absorption

The general consensus of opinion favors the view that the bulk flow of CSF occurs largely through arachnoid projections into the cranial and spinal venous systems (reviewed in Ref. 7). These are illustrated schematically in Fig. 1. Of course, there are other possible routes and mechanisms by which specific molecules can be removed from the cranial vault. For example, certain metabolic products can be absorbed actively by the choroid plexus (10).

First identified by Pacchioni in the 18th century, the microscopic arachnoid villi and macroscopic arachnoid granulations are herniations of the cranial arachnoid membrane that project into the venous sinuses of the dura mater on the convexity of the brain. The hydrostatic pressure difference between the CSF compartment and the venous sinuses is the driving force for absorption. An arachnoid stalk connects the subarachnoid space with the core of the arachnoid villus or

granulation. The stalk is composed of arachnoid cells and interdigitating processes, which protrude through the meningeal layer of the dura mater. Within the venous sinus the bulbous core of the arachnoid projection is made up of arachnoid cells within a trabeculated meshwork. The core is surrounded by a layer of endothelium that is continuous with the endothelial lining of the venous sinus. In addition, there are clusters of arachnoidal cells adjacent to the emerging spinal nerve roots that are attached to and also penetrate the dura of the root sleeves extending into small spinal veins.

The means by which CSF transports through these structures remains controversial, but suggested mechanisms include arachnoid cell phagocytosis, pressure-dependent pinocytosis, transport via giant vacuoles and/or transcellular channels, gaps between endothelial cells, passive transport via the extracellular cisterns of the arachnoid cell layer, or a labyrinth of open tubes that are presumed to connect the subarachnoid space with the venous sinuses in the dura.

Problems with current concepts

The notion that CSF is formed largely in the choroid plexus and is absorbed primarily through arachnoid villi and granulations provides the foundation for our current understanding of CSF physiology and is a central element in any consideration of the pathophysiology of hydrocephalus. However, it would seem that the experimental and clinical evidence favoring this view is far from persuasive (discussed in Refs. 11 and 17). Limited space does not permit a detailed discussion of this issue, but the following points summarize some of the difficulties in reconciling physiological and pathophysiological realities with an arachnoid projection-centric view of CSF absorption.

- Evidence supporting a role for arachnoid projections in CSF transport is primarily based on anatomic considerations. Support from quantitative data is limited.
- The mechanism of CSF transport through these structures remains speculative even after many years of investigation.
- Some arachnoid projections are not associated with veins. Whether these elements function to absorb CSF is unknown.

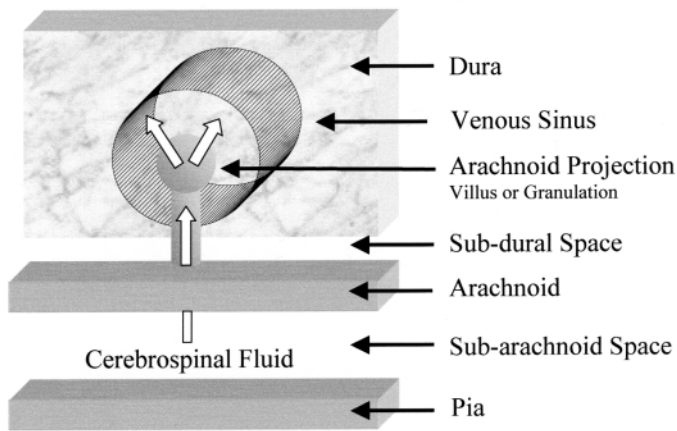


FIGURE 1. Schematic illustrating the conventional view of cerebrospinal fluid (CSF) transport. CSF is absorbed from the subarachnoid compartment through arachnoid villi or granulations that project into the dural venous sinuses.

- In rats, a CSF-venous sinus pressure gradient favoring absorption does not seem to exist until 20 days after birth. Without this pressure gradient, CSF must be absorbed at other locations or via mechanisms unrelated to arachnoid projections.
- There is little clear evidence linking developmental deficiencies of arachnoid projections with hydrocephalus.
- Perhaps the greatest impediment to the acceptance of the conventional view is the observation that arachnoid villi or granulations do not appear to exist prenatally. In two microscopic studies of autopsy specimens from individuals up to 56 days old (16) and from 18 wk of gestation to 80 yr (8), no arachnoid villi or granulations were observed before birth. The choroid plexus develops relatively early in gestation, and by the third gestational month it nearly fills both of the lateral ventricles (10). This suggests significant CSF production in the fetus and implies that the neonate has need of effective mechanisms to absorb CSF. It seems unlikely that arachnoid projections play a significant role at this level of development. However, at or around the time of birth, arachnoid projections start to become visible in the dura (9). As the infant ages, the villi and granulations increase in number, and in the adult they exist in abundance. Therefore, arachnoid projections may have some role in CSF transport in the older individual.

An alternative notion: a role for extracranial lymphatic vessels

Although the central nervous system parenchyma does not contain lymphatic vessels, numerous studies suggest a physiological link between cerebral interstitial fluid, CSF, and extracranial lymph. Protein tracers injected into the brain interstitium or CSF exit the cranium and enter lymphatic vessels. The injected molecules pass out of the cranium along the prolongations of the subarachnoid space associated with several cranial nerves. The observation that tracers injected into the ventricles enter the spinal lymph nodes suggests that similar CSF-to-lymph pathways exist in the spinal cord as well.

Although there are many potential locations where CSF

may gain access to extracranial lymphatic vessels, most attention has focused on the cribriform plate and the nasal submucosa. The bony cribriform plate is located at the base of the anterior skull and supports the olfactory bulbs. Olfactory nerves penetrate this bone through holes or foramina and terminate in the olfactory epithelium in the nasal mucosa. Investigators have known for some time that CSF convects along the extensions of the subarachnoid compartment associated with the olfactory nerves, transports through the cribriform plate, and is ultimately absorbed by lymphatics in the nasal submucosa (6, 12). Morphological evidence also supports the cribriform/lymphatic CSF transport pathway in humans and nonhuman primates (discussed in Ref. 17). In some species, the perineural extensions of the subarachnoid space appear to open directly into the tissue spaces from which CSF is absorbed into prenodal lymphatics. In rats, CSF passes directly from arachnoid channels into nasal lymphatics (12). The cervical lymphatic ducts in the neck transport CSF back to the venous system. The concept of CSF transport into extracranial lymphatic vessels is illustrated in Fig. 2.

Volumetric CSF transport into extracranial lymphatic vessels

Quantitative methods employing radioactive protein tracers and mathematical modeling have been developed to estimate the clearance of CSF through extracranial lymphatics and nonlymphatic routes in sheep and rats. An important element in the design of the model was the ability to correct the recovery data for errors introduced by filtration of the CSF tracer. Plasma recoveries of the CSF tracer in lymph-diverted animals were used to estimate nonlymphatic absorption (arachnoid projection transport?). The nonlymphatic contribution to CSF clearance would be underestimated if the loss of CSF tracer due to the normal filtration of proteins from the vasculature was not taken into consideration. Similarly, the lymphatic contribution to CSF drainage would be overestimated due to the transport of the CSF tracer to plasma with subsequent reentry of the tracer into lymph. Therefore, without correction the relevant lymphatic vessels might receive CSF tracer not only from the CSF compartment directly but also from recirculated plasma tracer.

With these factors accounted for mathematically, the data suggested that nearly one-half of all CSF removed from the extracranial compartment in adult sheep was cleared by lymphatics (2–4). Therefore, extracranial lymphatic vessels appeared to have a major role in CSF volumetric clearance in this species.

To continue on this theme, elevations of intracranial pressure (ICP) were observed to increase CSF transport into cervical lymphatics (1). Indeed, cervical lymphatic pressures and flow rates were related closely to ICP (18). At baseline CSF pressures, ~10% of the lymph in the cervical lymphatic vessels had its origins as CSF. As ICP was elevated, the proportion increased. At 70 cmH₂O ICP, cervical lymph flow rates were fourfold higher compared with baseline conditions, and nearly 80% of the lymph in these ducts was estimated to originate in the CSF compartment at this pressure.

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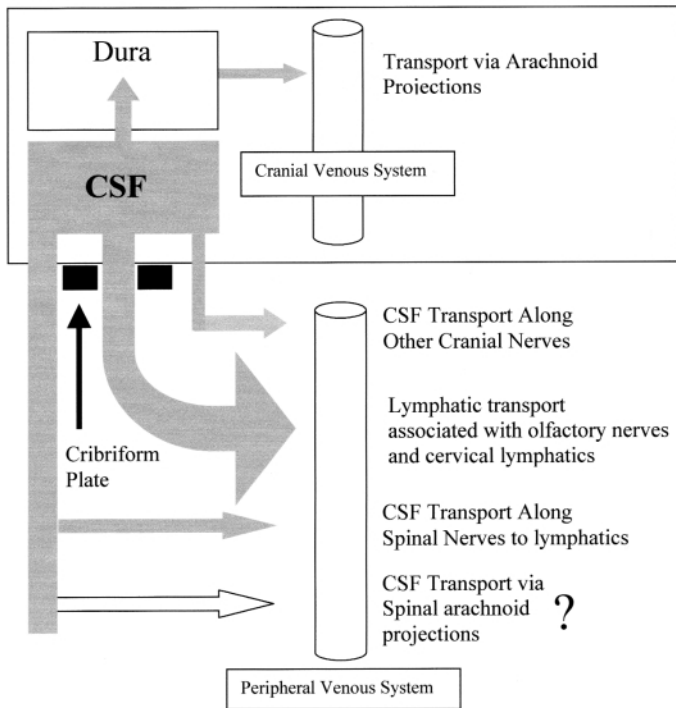


FIGURE 2. Schematic illustrating CSF transport from the cranial and spinal subarachnoid compartments into extracranial lymphatic vessels.

Since increases in ICP have a significant effect on cervical lymph dynamics, it seems logical to assume that interruption of CSF lymph transport would impact cranial physiology. This issue has been very difficult to study experimentally because it is virtually impossible to block every potential CSF-lymph connection. Many if not most cranial and spinal nerves may be involved in this process. Likewise, blocking one CSF transport pathway from the cranium may lead to the recruitment of additional absorption sites, such as those located in the spinal cord. The possible induction of new extracranial drainage pathways would tend to blunt the effects of the chosen intervention. It is not surprising, therefore, that early attempts to obstruct selected lymphatic vessels produced inconsistent effects on intracranial physiology.

However, a different approach has recently been used to test this concept. The cribriform plate represents a discrete site that can be accessed extracranially. A method was devised to interrupt CSF transport into the nasal submucosa surgically by sealing the extracranial surface of the cribriform plate with glue or bone wax (13). An important element of the experimental design was the separation of the cranial and spinal subarachnoid compartments. With this method, cranial CSF absorption could be assessed without the added complexities of compensatory CSF transport mechanisms associated with the spinal cord (5). CSF parameters in the same animal were compared before and after obstructing this pathway, and several concepts emerged.

First, under normal conditions, the ongoing production of CSF is matched by CSF drainage, such that ICP remains stable. After the cribriform plate was obstructed, baseline ICP was elevated. Mean, diastolic, and systolic ICPs doubled when CSF transport through the cribriform plate was prevented (14). Therefore, with a major absorption site negated, the ability of

the host to balance CSF production was impaired. To establish a new equilibrium condition, much higher ICPs were required.

Second, following bolus infusions of saline into the CSF compartment of adult sheep, obstruction of CSF transport through the cribriform plate increased the peak ICP after infusion and augmented the time required for ICP to return to baseline. Analysis of the data indicated that CSF outflow resistance was elevated significantly (17).

Third, cribriform plate obstruction reduced cranial CSF absorption (13). This concept is illustrated in Fig. 3. For a given ICP, CSF clearance was reduced substantially after sealing the cribriform plate (Fig. 3A). In addition, it is evident that much higher CSF pressures were required to maintain a given CSF absorption rate when CSF access to lymphatic vessels in the nasal submucosa was prevented (Fig. 3B). Remarkably, in adult animals with spinal compensation accounted for, the data suggested that the majority of cranial CSF transport occurred through the cribriform plate at low CSF pressures and that other undefined clearance sites were recruited only when pressures were elevated.

It is evident therefore that extracranial lymphatics play an important role in volumetric CSF transport in the adult animal. However, the importance of this pathway earlier in development is still unresolved. As noted above, there is some evidence that arachnoid projections are absent or poorly developed before birth. Therefore, it is possible that lymphatic vessels play an even more important role in CSF transport in the neonate.

To begin to address this issue, CSF transport (conductance) and CSF outflow resistances were compared in late-gestation fetal and adult sheep (15). No significant differences in CSF conductance or CSF outflow resistance were observed (Fig. 4). Additionally, when a radioactive CSF protein tracer was injected into the CSF compartment of fetal animals, the highest concentrations were measured from the cervical lymphatics compared with those observed in plasma or thoracic duct lymph. Therefore, global CSF transport parameters in the late

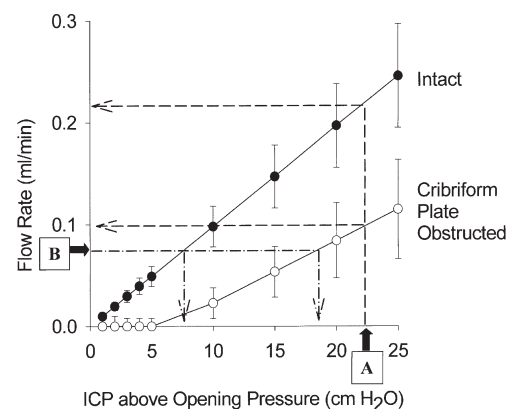


FIGURE 3. Relationship between intracranial pressure (ICP) and flow rate (CSF absorption). CSF access to the spinal subarachnoid compartment was prevented. Data has been replotted from Ref. 13. Closed circles represent data obtained before and open circles represent data obtained after the cribriform plate had been sealed. Opening pressure was the estimated threshold pressure at which CSF absorption was induced.

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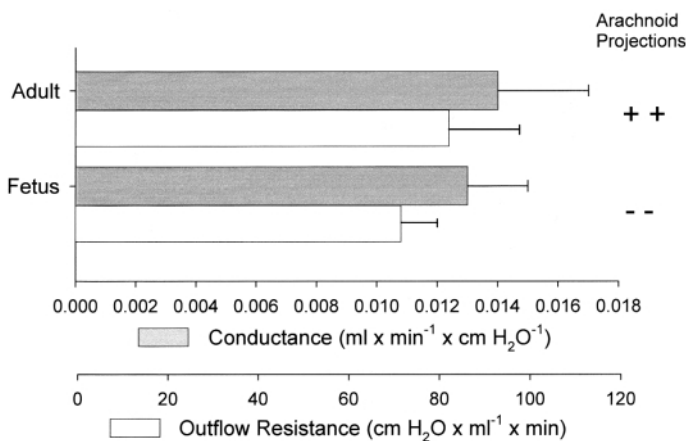


FIGURE 4. Comparison of CSF conductance and CSF outflow resistance in fetal and adult sheep. Data replotted from Ref. 15.

gestation-fetal and adult sheep were very similar, despite the fact that arachnoid projections exist in substantial numbers only in the adult. These experiments demonstrated a function for lymphatics in fetal CSF transport and suggested that arachnoid projections might play a limited role earlier in development.

Understanding CSF transport in hydrocephalus: relevance of absorptive mechanisms

In this review, some fundamental issues related to the biomechanics of CSF absorption have been discussed. Since the drainage of central nervous system extracellular liquid was assumed to occur through the arachnoid projections, there seemed little need to incorporate lymphatics into the conceptual framework that has driven investigation in this area. However, there is considerably more quantitative data indicating an important role for extracranial lymphatic vessels in CSF absorption than exists to support a role for arachnoid projections. One cannot doubt the existence of arachnoid projections, at least after birth. However, to understand their function, quantitative studies will have to be designed to address their role in CSF transport. With further investigation, it may be possible to integrate our understanding of the various transport pathways and their operational pressure ranges in such a way as to provide a foundation on which to build new hypotheses that probe the pathogenesis of hydrocephalus.

Hydrocephalus is a complex disorder involving the accumulation of CSF and ventricular dilation. This disease continues to represent a significant neurosurgical challenge, and considerable effort has been directed to the design and manufacture of new shunts to facilitate CSF diversion. Remarkably, there has been much less effort directed at the fundamentals of CSF absorption, presumably because the relevant pathways and mechanisms were thought to have been elucidated. It would now appear that we have much to learn about CSF transport and that current concepts may be in need of revision. Although it is unlikely that hydrocephalus relates simply to an imbalance between CSF production and absorption, impediments to CSF transport out of the brain and spinal cord are undoubtedly involved in the pathogenesis of this disease. It will be difficult to conceptualize the development of new

therapies to treat hydrocephalus in its various forms without first having a clear understanding of the transport parameters and pathways associated with normal CSF absorption. Further investigation of this neglected area seems warranted.

References

1. Boulton M, Armstrong D, Flessner MF, Hay JB, and Johnston MG. Raised intracranial pressure increases CSF drainage through arachnoid villi and extracranial lymphatics. *Am J Physiol Regul Integr Comp Physiol* 275: R889–R896, 1998.
2. Boulton M, Armstrong D, Mohamed R, Flessner M, Hay J, and Johnston MG. Relative contribution of arachnoid villi and extracranial lymphatics to the clearance of a CSF tracer in the rat. *Am J Physiol Regul Integr Comp Physiol* 276: R818–R823, 1999.
3. Boulton M, Flessner M, Armstrong D, Hay JB, and Johnston M. Lymphatic drainage of the CNS: effects of lymphatic diversion/ligation on CSF protein transport to plasma. *Am J Physiol Regul Integr Comp Physiol* 272: R1613–R1619, 1997.
4. Boulton M, Flessner M, Armstrong D, Hay J, and Johnston M. Determination of volumetric cerebrospinal fluid absorption into extracranial lymphatics in sheep. *Am J Physiol Regul Integr Comp Physiol* 274: R88–R95, 1998.
5. Bozanovic-Sosic R, Mollanji R, and Johnston MG. Spinal and cranial contributions to total cerebrospinal fluid transport. *Am J Physiol Regul Integr Comp Physiol* 281: R909–R916, 2001.
6. Bradbury MWB and Cserr HF. Drainage of cerebral interstitial fluid and cerebrospinal fluid into lymphatics. In: *Experimental Biology of the Lymphatic Circulation*, edited by Johnston MG. Amsterdam: Elsevier Science, 1985, p. 355–394.
7. Davson H and Segal MB. *Physiology of the CSF and blood-brain barriers*. Boca Raton, FL: CRC, 1996.
8. Fox RJ, Walji AH, Mielke B, Petruk KC, and Aronyk KE. Anatomic details of intradural channels in the parasagittal dura: a possible pathway for flow of cerebrospinal fluid. *Neurosurgery* 39: 84–91, 1996.
9. Gomez DG, Ehrmann JE, Potts DG, Pavese AM, and Gilanian A. The arachnoid granulation of the newborn human: an ultrastructural study. *Int J Dev Neurosci* 1: 139–147, 1983.
10. Johanson CE. Ventricles and cerebrospinal fluid. In: *Neuroscience in Medicine*, edited by Conn PM. Philadelphia: J. B. Lippincott, 1995, p. 171–196.
11. Johnston M, Boulton M, and Flessner M. Cerebrospinal fluid absorption revisited: do extracranial lymphatics play a role? *Neuroscientist* 6: 77–80, 2000.
12. Kida S, Pantazis A, and Weller RO. CSF drains directly from the subarachnoid space into nasal lymphatics in the rat. Anatomy, histology and immunological significance. *Neuropathol Appl Neurobiol* 19: 480–487, 1993.
13. Mollanji R, Bozanovic-Sosic R, Silver I, Li P, Kim C, Midha R, and Johnston MG. Intracranial pressure accommodation is impaired by blocking pathways leading to extracranial lymphatics. *Am J Physiol Regul Integr Comp Physiol* 280: R1573–R1581, 2001.
14. Mollanji R, Bozanovic-Sosic R, Zakharov A, Makarian L, and Johnston MG. Blocking cerebrospinal fluid absorption through the cribriform plate increases resting intracranial pressure. *Am J Physiol Regul Integr Comp Physiol* 282: R1593–R1599, 2002.
15. Mollanji R, Papaiconomou C, Boulton M, Midha R, and Johnston MG. Comparison of cerebrospinal fluid transport in fetal and adult sheep. *Am J Physiol Regul Integr Comp Physiol* 281: R1215–R1223, 2001.
16. Osaka K, Handa H, Matsumoto S, and Yasuda M. Development of the cerebrospinal fluid pathway in the normal and abnormal human embryos. *Child's Brain* 6: 26–38, 1980.
17. Silver I, Kim C, Mollanji R, and Johnston MG. Cerebrospinal fluid outflow resistance in sheep: impact of blocking CSF transport through the cribriform plate. *Neuropathol Appl Neurobiol* 28: 67–74, 2002.
18. Silver I, Li B, Szalai JP, and Johnston MG. Relationship between intracranial pressure and cervical lymphatic pressure and flow rates in sheep. *Am J Physiol Regul Integr Comp Physiol* 277: R1712–R1717, 1999.

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