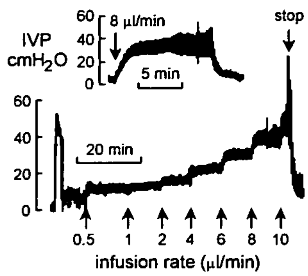
Cerebrospinal Fluid Out Flow Dynamics

Continuous infusion method
(Davson H et al, Brain 1970)

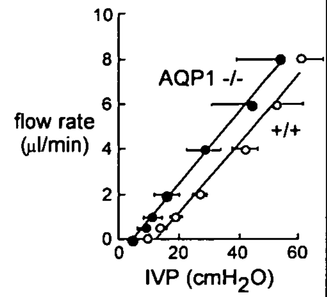
IVP was monitored during continuous perfusion of fluid into the lateral ventricle. The each flow-rate increased the pressure and achieved a steady-state (as like as right Fig.).



Results

Pressure-flow curves were constructed for each studies and later averaged for mice of the same genotype (n=6). The slopes were estimated the CSF outflow and analysed.

--> The slope was no different between the wild-type and AQP1 null mice (7.15 ± 2.93 vs. 6.42 ± 3.06, respectively).

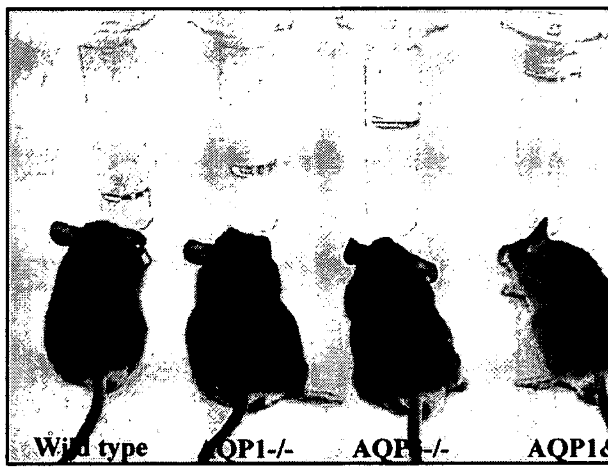


Summary

- There is no differences in morphology of choroid plexus epithelium between wild type mice and AQP1 null mice.
- AQP1 deletion reduced 5-fold in Osmotic permeability of Choroid plexus epithelium.
- AQP1 contributes to 20-25% of total CSF production.
- AQP1 deletion reduced the intra-ventricle pressure with 60%.
- Continuous infusion method indicated CSF outflows were same level between the wild-type and AQP1 null mice.

↓

Why IVP was reduced 60% by AQP1 deletion ?

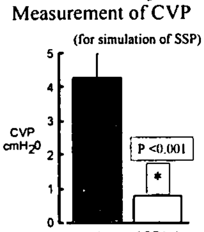


$$ICP = I_f \times R_{out} + P_{ss}$$

Marmarou et al. (1978)

I_f : CSF formation rate
R_{out} : the resistance to outflow of CSF
P_{ss} : the sagittal sinus pressure

Measurement of CVP
(for simulation of SSP)



Summary

- I_f : 25% difference
- R_{out} : no difference
- P_{ss} : 3cmH2O difference

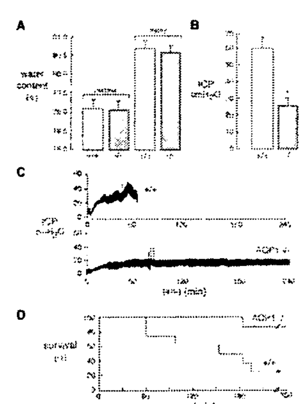
⇩

IVP 60% reduction

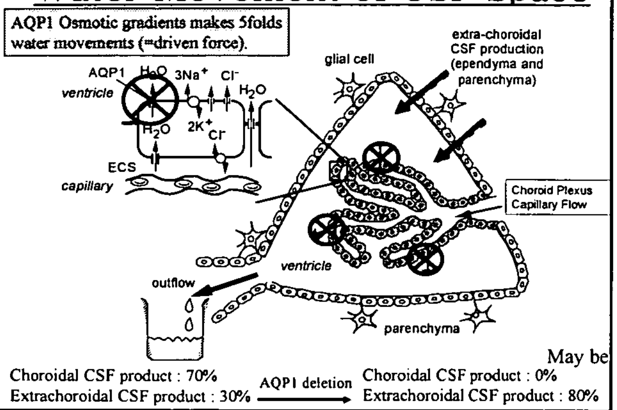
Freeze injury in AQP1 null mice

AQP1 deletion does not reduce vasogenic edema. Whereas ICP was decreased compare with WT mice.

→why?
Reduction of CSF driving force.



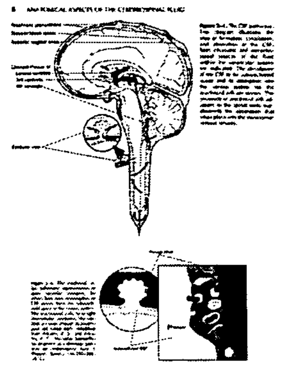
Water Movement of CSF Space



CSF absorption

predominant absorption route

1. Subarachnoid space → arachnoid villi → dural sinus hydrostatic pressure difference between CSF pressure and dural sinus pressure
2. Trans-ependymal and parenchymal water and ion movement



Accelerated progression of kaolin-induced hydrocephalus in aquaporin-4-deficient mice

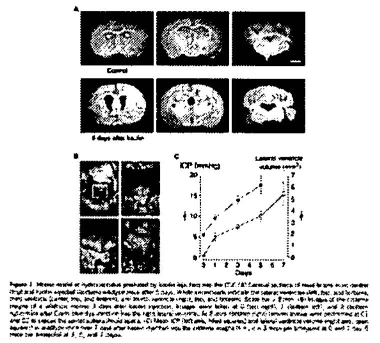
Olin Bloch[1], Kurtis I Auguste[1,2], Geoffrey T Manley[2] and AS Verkman[1]

Hydrocephalus is caused by an imbalance in cerebrospinal fluid (CSF) production and absorption, resulting in excess ventricular fluid accumulation and neurologic impairment. Current therapy for hydrocephalus involves surgical diversion of excess ventricular fluid. The water-transporting protein aquaporin-4 (AQP4) is expressed at the brain–CSF and blood–brain barriers. Here, we provide evidence for AQP4-facilitated CSF absorption in hydrocephalus by a transparenchymal pathway into the cerebral vasculature. A mouse model of obstructive hydrocephalus was created by injecting kaolin (2.5 mg/mouse) into the cisterna magna. Intracranial pressure (ICP) was ~5 mm Hg and ventricular size <0.3 mm³ in control mice. Lateral ventricle volume increased to 3.7±0.5 and 5.1±0.5 mm³ in AQP4 null mice at 3 and 5 days after injection, respectively, significantly greater than 2.6±0.3 and 3.5±0.5 mm³ in wildtype mice (P<0.005). The corresponding ICP was 22±2 mm Hg at 3 days in AQP4 null mice, significantly greater than 14±1 mm Hg in wildtype mice (P<0.005). Brain parenchymal water content increased by 2% to 3% by 3 days, corresponding to ~50 μL of fluid, indicating backflow of CSF from the ventricle into the parenchymal extracellular space. A multi-compartment model of hydrocephalus based on experimental data from wildtype mice accurately reproduced the greater severity of hydrocephalus in AQP4 null mice, and predicted a much reduced severity if AQP4 expression/function were increased. Our results indicate a significant role for AQP4-mediated transparenchymal CSF absorption in hydrocephalus and provide a rational basis for evaluation of AQP4 induction as a nonsurgical therapy for hydrocephalus.

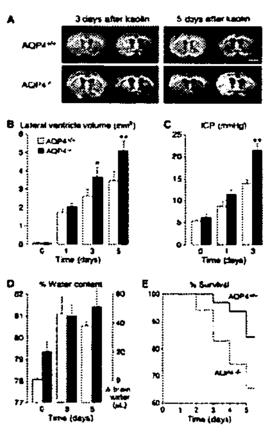
Keywords: AQP4; blood-brain barrier; hydrocephalus; interstitial edema; water channel

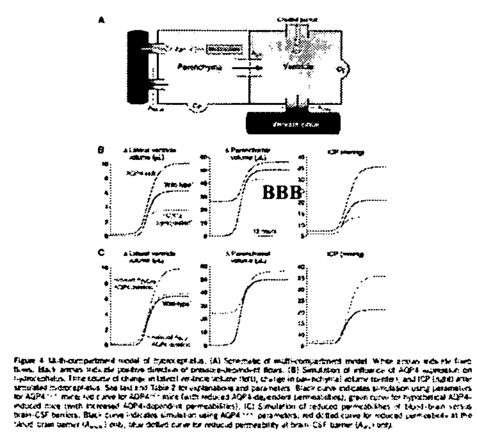
- AQP4 deletion makes "Bad" Hydrocephalus. Why?

Kaolin induced hydrocephalus model



WT vs AQP4-/-

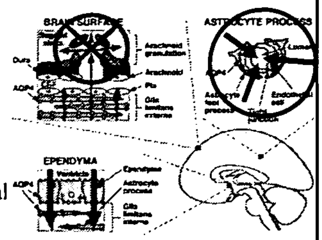




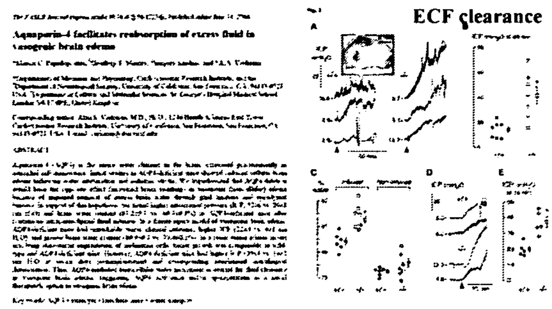
Mechanism of compensation CSF outflow

- Normal CSF Out flow
  - [redacted]
  - AQP4 dependent transparenchymal water clearance into the cerebral vasculature.

Compensation

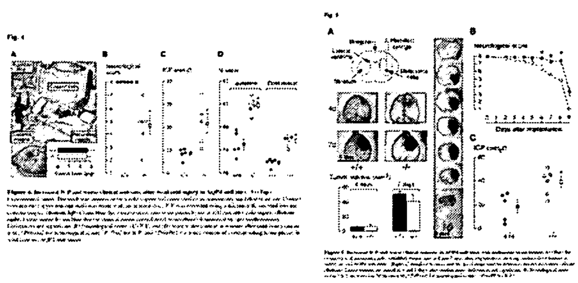


Vasogenic edema (ECF ↑)



Papadopoulos et al. 2004

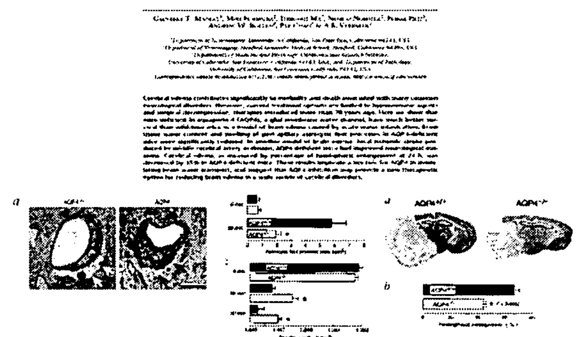
Models of vasogenic edema produced by cortical freeze injury or brain tumor, AQP4 deletion worsens the severity of the edema.



Papadopoulos et al. 2004

Cellular edema

Aquaporin-4 deletion in mice reduces brain edema after acute water intoxication and ischemic stroke



Manley et Al 2000

AQP4 deletion

1. Decreased Cellular edema
   - Reduced water movement from ECF to astrocyte endofoot.
2. Increased Vasogenic Edema & Interstitial edema
   - Reduced water movement from ECF to astrocyte (BBB)

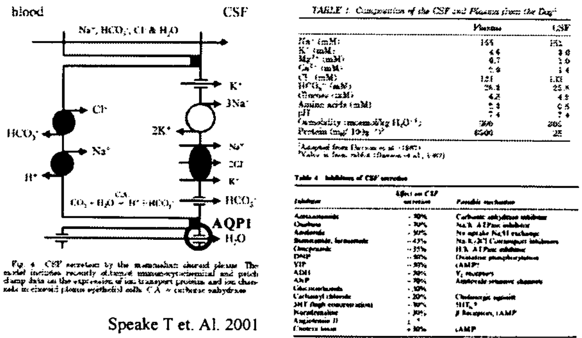
AQP4 may facilitate the clearance of excess Extra Cerebral Fluid (ECF) = Bulk Flow CSF.

CSF circulation

CSF flow speed = apploximetry 0.35ml/min

1. Choroidal CSF driving force(7-11mmHg)
2. CSF pulsation (choroidal arterial pulse & respiratory change of ICP)
3. Difference between CSF pressure & dural sinus pressure (3.5−7mmHg)

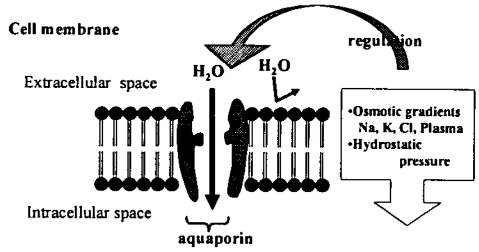
Mechanisms of CSF Secretion by the Choroid Plexus



Speake T et. Al. 2001

Segal 1993

Conclusion



- Membrane water permeability is not so high if there is no aquaporin.
  Water does not move so fast if there is no aquaporin.
- CSF "Pressure" depends on speed of moving water in (AQP1) & out (AQP4) .

Conclusion

1. The reduced ICP and CSF production in AQP1 null mice provides direct functional evidence for the involvement of AQP1 in CSF dynamics, suggesting AQP1 inhibition as a novel option for therapy of elevated ICP and one of the type of hydrocephalus.
2. AQP4 may facilitate the clearance of excess Extra Cerebral Fluid (ECF) = Bulk Flow CSF. These results provide a rational basis for evaluation of AQP4 induction as a nonsurgical therapy for hydrocephalus.

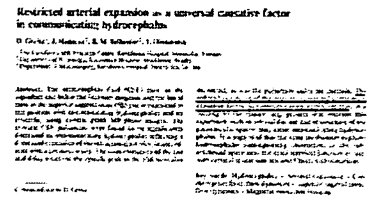
Rethinking the physiology of CSF circulation and hydrocephalus:

Do we finally understand normal pressure hydrocephalus?

Summer workshop for iNPH
Sakura City, September 25th – 26th, 2007

Dan Greitz
Dept. of Neuroradiology
Karolinska University Hospital
Stockholm, Sweden

The hydrodynamic concept of hydrocephalus was first presented in 1994 at the Symposium Neuroradiologicum XV in Kumamoto


Restricted arterial expansion as a universal causative factor in communicating hydrocephalus

In: Proceedings of SNR XV, Neuroradiology [suppl] 37:14-18;1995

Basic mechanisms and major differences between the new and old concept

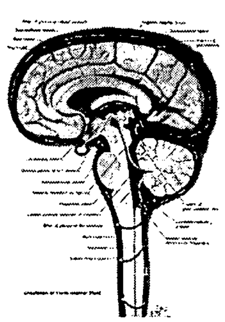
1. **CSF circulation**
2. **Hydrocephalus**
3. **New implications**

Major differences
between the new and old concept

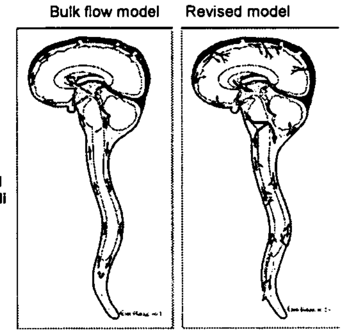
1. **CSF circulation**
2. **Hydrocephalus**
3. **New implications**

Normal CSF circulation old CSF bulk flow model

- **There is bulk flow of CSF from the intraventricular plexus to the arachnoid villi**



The CSF Circulation

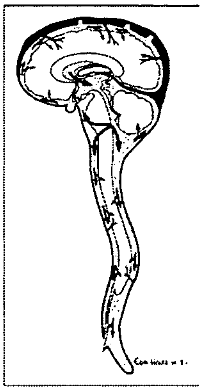


D Greitz 1993

Current Concept of the CSF Circulation

The CSF is absorbed by the brain capillaries

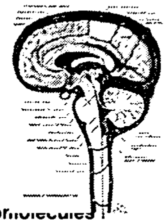
– not by the arachnoid villi



D Greitz 1993

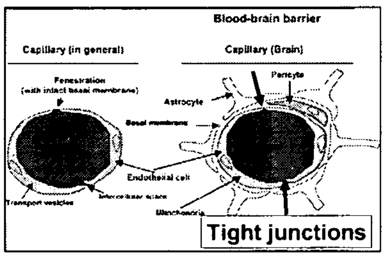
The CSF bulk flow model

is based on the assumption that the arachnoid villi absorb all proteins and macromolecules in the CNS and that –



brain capillaries are impermeable to macromolecules !

Blood-brain barrier



Due to the tight junctions, the BBB is almost impermeable to proteins and other macromolecules

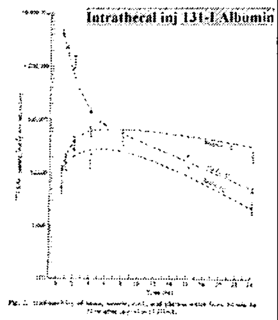
Can they pass in the other direction from brain-to-blood?

Albumin transport from CSF to blood

Rapid elimination of albumin from the CSF

Rapid transport of albumin from CSF to plasma – half-time max in plasma occurs at 90 min

Rapid transport of albumin from the CSF into the brain



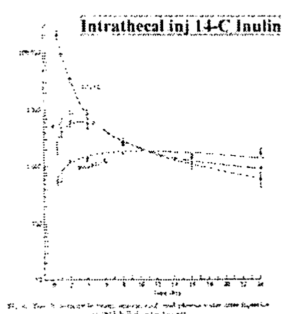
Reed & Woodbury: J Physiol 1963

Inulin transport from CSF to blood

Rapid elimination of inulin from the CSF

Rapid transport of inulin from CSF to plasma – half-time max in plasma 60 min

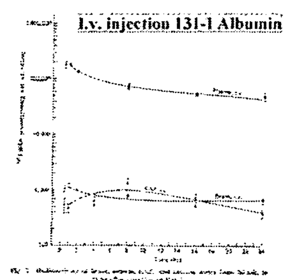
Rapid transport of inulin from the CSF into the brain



Reed & Woodbury: J Physiol 1963

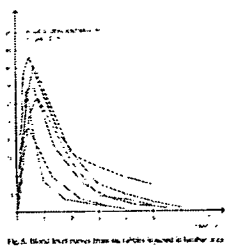
Albumin transport from blood to CSF

After i.v. injection, there is a small but significant transport of albumin from the blood to the CSF and to the brain



Reed & Woodbury: J Physiol 1963

Absorption of contrast medium from CSF to blood



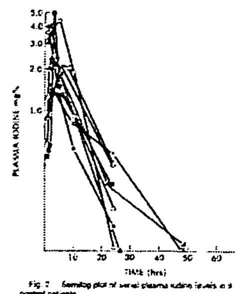
Blood concentration curve

At myelography in rabbits, there is a rapid transport of contrast from CSF to blood

Peak concentration in blood occurs within 1 hour

Golman K: Neuroradiology 1979

Absorption of contrast medium from CSF to blood



Blood concentration curve

At myelography in humans, there is a rapid transport of contrast from CSF to blood

Peak concentration in blood occurs within 2 hours

Enzmann D: Radiology 1979

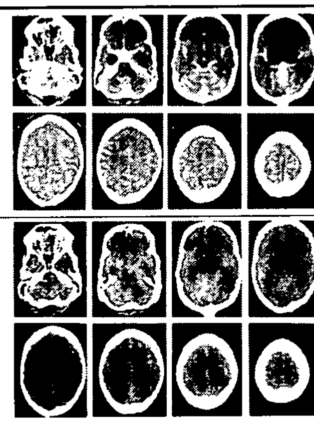
Rapid transport of contrast medium into the brain cortex

1 hour after i.c. injection in rabbit

Sage M: AJR 1983

CT-cisternography

3 hours



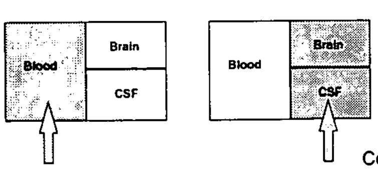
At 3 hours, there is penetration of the contrast medium into the brain cortex

24 hours

At 24 hours, almost all contrast is located in brain tissue

T. Hindmarsh

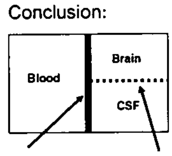
Blood brain barrier?



Non diffusible colour tracer

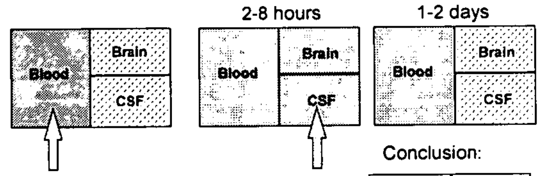
Ehrlich 1885 and Goldmann 1913

Conclusion:



Blood brain barrier

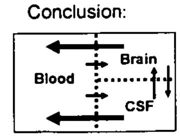
2-8 hours 1-2 days



Inulin, albumin, Iodine, contrast media

Reed & Woodbury 1963

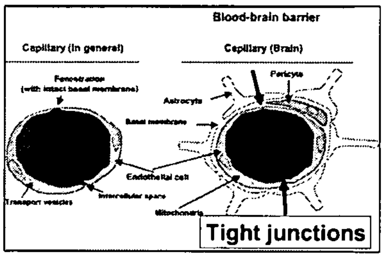
Conclusion:



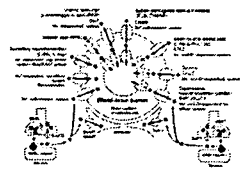
Rapid transport from CNS to blood

D Greitz 1993

What is the biological substrate for the active transport at the BBB ?



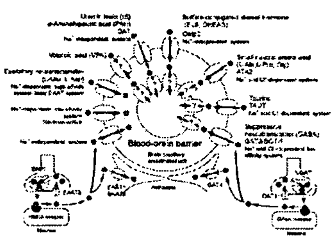
Several brain to blood efflux transporters have been discovered at the BBB



- Betz discovered the first efflux transporter of amino acids (1978)
  - since then 40 different efflux transporters have been identified
- Significant increase in publications on efflux: 60 papers (1978 to 2000) 250 papers (2000 to 2007)

(Search PubMed "BBB & Efflux")

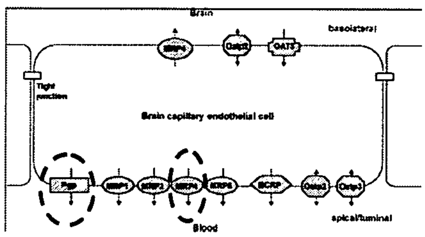
Brain to blood efflux transporters



transport numerous of endogenous and exogenous macromolecules

"The BBB acts as a dynamic regulatory interface" (Comford 1985)

Brain-to-blood efflux transporters



Immuno-fluoroscence studies of P-glycoprotein and Multidrug Resistance Protein (MRP4)

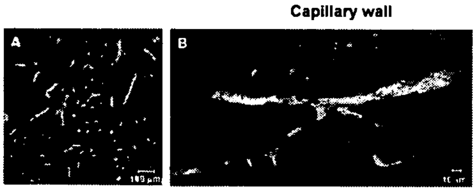
Löscher 2005

Review

Recent advances in the brain-to-blood efflux transport across the blood-brain barrier

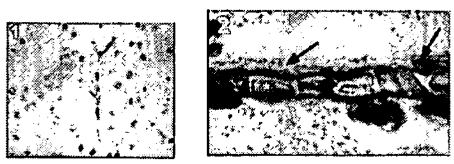
Ken-ichi Hosoya, Sumio Ohtsuki, Tetsuya Terasaki

Capillary wall



Multidrug transporter P-glycoprotein (fluoroscence green)

Mrp4 Confers Resistance to Topotecan and Protects the Brain from Chemotherapy



Capillary   Capillary wall

Multidrug Resistance Protein (MRP4 in red)

ELSEVIER

Advanced Drug Delivery Reviews 36 (1999) 175–209

advanced drug delivery reviews

The blood–brain barrier efflux transporters as a detoxifying system for the brain

Tetsuya Terasaki*, Ken-ichi Hosoya

The efflux transporters act as a detoxifying system for the brain

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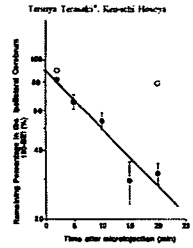
The blood–brain barrier efflux transporters as a detoxifying system for the brain

Tetsuya Terasaki*, Ken-ichi Hosoya

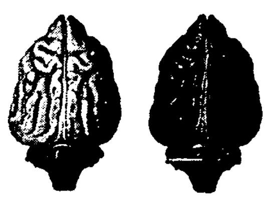
Half-time disappearance rate from brain:

12 min for PAH



p-Aminohippuric acid (PAH)

Historical evidence of CSF absorption by capillaries



Even in 1914,
Dandy and Blackfan performed colour tracer studies

CSF absorption by capillaries in 1914

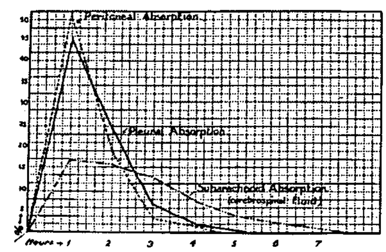


Fig. 7.—Curves to compare the total excretion of peritoneal, pleural and cerebrospinal fluids. The base line represents time divided into one-hour intervals. The vertical line represents absorption (percentage of excretion) of phenolsulphonephthalein in the urine.

Dandy and Blackfan injected a colour tracer (phenolsulphonphthalien) intrathecally and measured its concentration in urine

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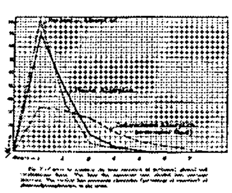
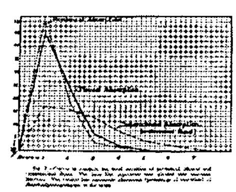
CSF absorption by capillaries in 1914



Dandy and Blackfan disapproved of CSF absorption by the Pacchionian Granulations and stated:

CSF absorption by capillaries in 1914



"The curve of the subarachnoid absorption is not greatly dissimilar from that of the peritoneal or pleural cavities and in none of these cavities is it necessary to call on specialized structures to explain absorption of fluid"

Conclusions

1. The CSF is absorbed by brain capillaries – not by arachnoid villi
2. There is an asymmetric transport of proteins and macromolecules across the BBB
3. The transport from brain to blood is much faster than in the other direction

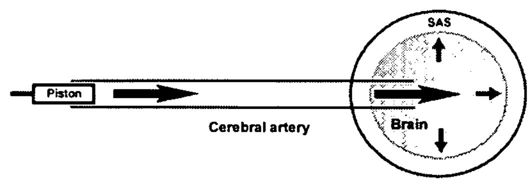
Major differences between the new and old concept

1. **CSF circulation**
2. **Hydrocephalus**
3. **New implications**

Hydrodynamic concept of hydrocephalus

Hydrodynamic theory

Communicating hydrocephalus



Increased intracerebral pulse pressure is the cause of communicating hydrocephalus

Hydrodynamic theory:

- Communicating hydrocephalus is caused by decreased intracranial compliance increasing the intracerebral pulse pressure

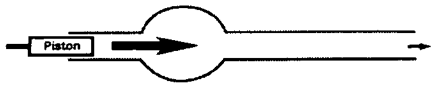
Compliance:

- is the "giving property" or the capacity of a volume change in a system
- is defined as volume change divided by pressure change

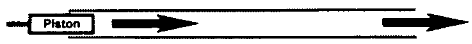
$$C = dV/dP$$

Pulse pressure transmission

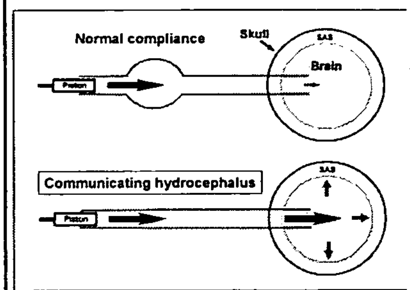
Compliant tubing



Non-compliant rigid tubing



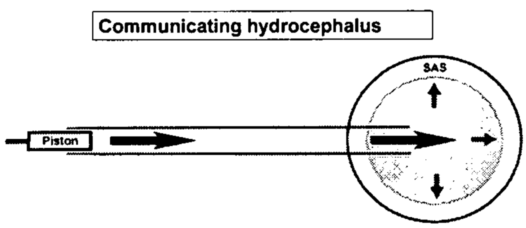
Pulse pressure transmission



In normal compliant artery, the artery dampens the pulse pressure transmission into the brain

Pulse pressure is transmitted undamped into the brain

The decreased compliance in communicating HC causes the cerebral artery to behave like a rigid tube



The transmitted pressure into the brain distends the brain and causes hydrocephalus

Is the CSF circulation a causative factor in communicating hydrocephalus?

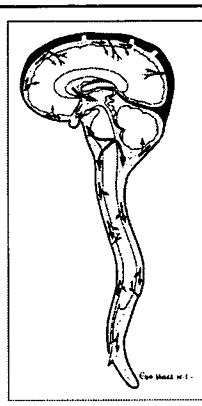
1. Revised model of CSF circulation

2. Bulk flow model of CSF circulation

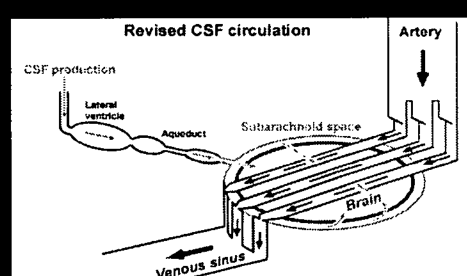
The CSF Circulation

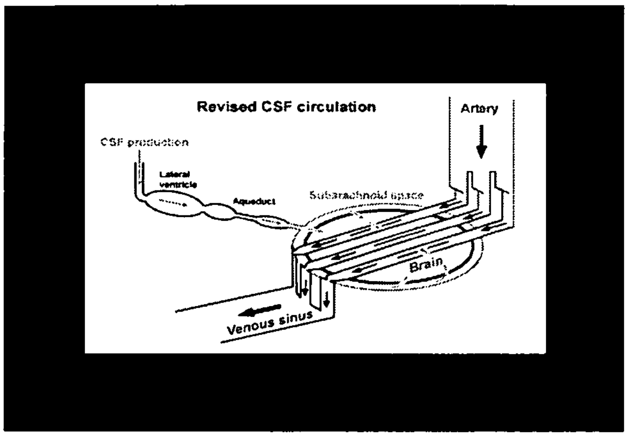
Revised model

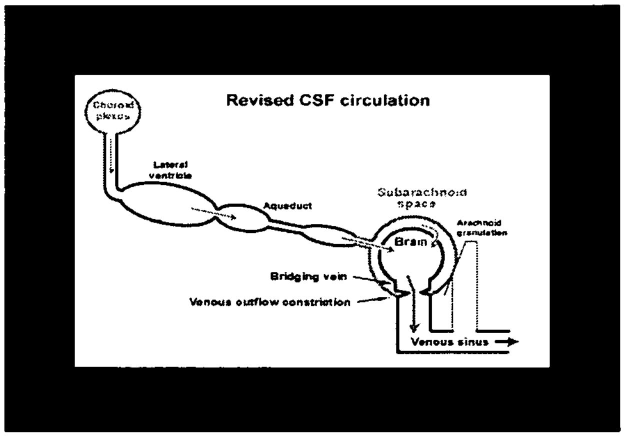
CSF is absorbed by the brain capillaries



D Greitz 1993

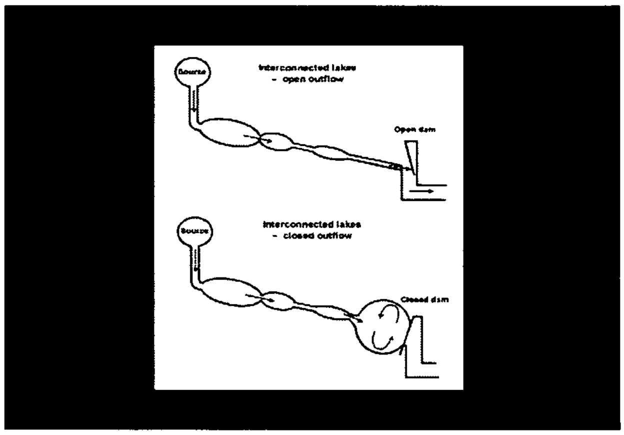


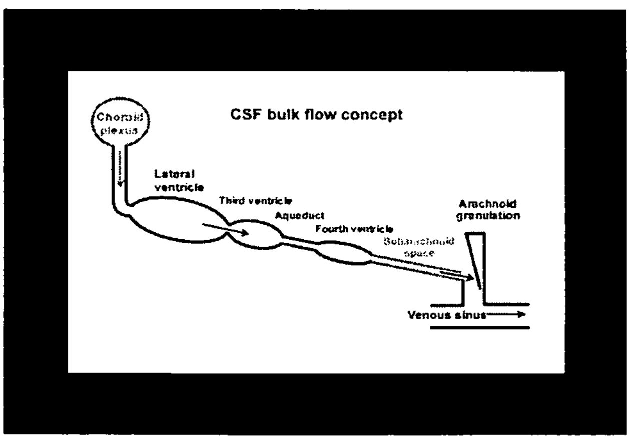


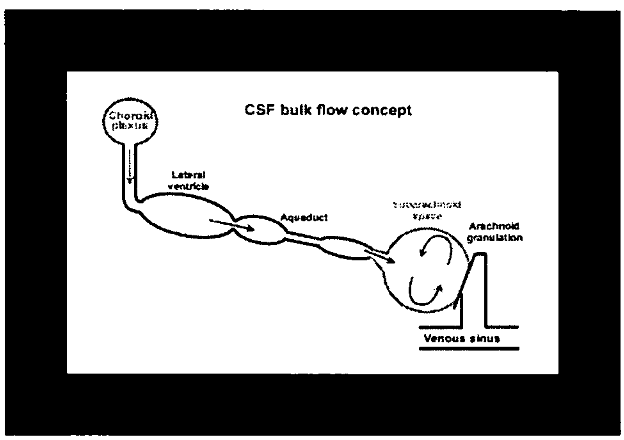


Is the CSF circulation a causative factor in communicating hydrocephalus?

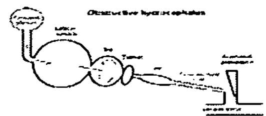
1. Revised model of CSF circulation
2. Bulk flow model of CSF circulation



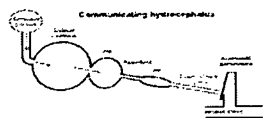




Obstructive hydrocephalus
is compatible with the
bulk flow concept



However,
Communicating hydrocephalus
is not compatible with the
bulk flow concept!



This was known by Dandy & Blackfan even in 1914

It remains a mystery why the bulk flow concept was applied to communicating hydrocephalus

Communicating hydrocephalus is not compatible with the CSF bulk flow concept:

With CSF obstruction at the arachnoid villi:

- The subarachnoid space should dilate – not the ventricles

Communicating hydrocephalus is not compatible with the CSF bulk flow concept:

With CSF obstruction at the arachnoid villi:

- Subarachnoid space should dilate – not the ventricles
- According to the law of Pascal, all intracranial pressure gradients including the transmantle pressure gradient should disappear

Communicating hydrocephalus is not compatible with the CSF bulk flow concept:

With CSF obstruction at the arachnoid villi:

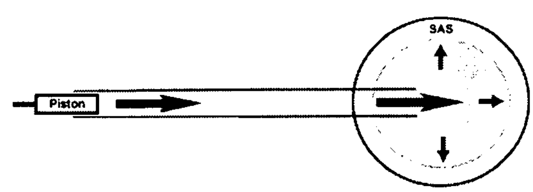
- The subarachnoid space should dilate – not the ventricles
- According to the law of Pascal, all pressure gradients including the transmantle pressure gradient should disappear
- Since CSF is incompressible – intracranial pressure must increase

This indicates that normal-pressure hydrocephalus is incompatible with the concept

Thus:

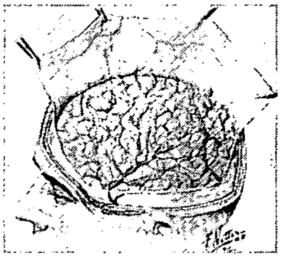
- In accord with the CSF bulk flow theory – acute obstructive hydrocephalus is caused by a CSF flow obstruction
- Communicating hydrocephalus must be caused by another mechanism than a CSF flow obstruction

Hydrocephalus



It is suggested that this mechanism is decreased compliance and increased pulse pressure

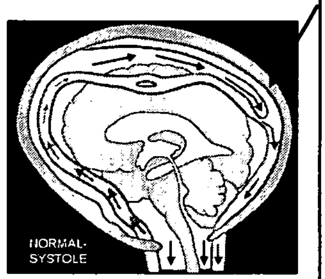
Bridging veins



The compliant veins are responsible for two thirds of intracranial compliance
The compliant thecal sac is responsible for one third of intracranial compliance

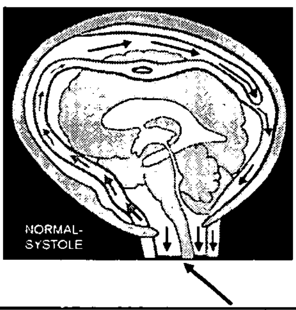
Normal compliance - Systole I

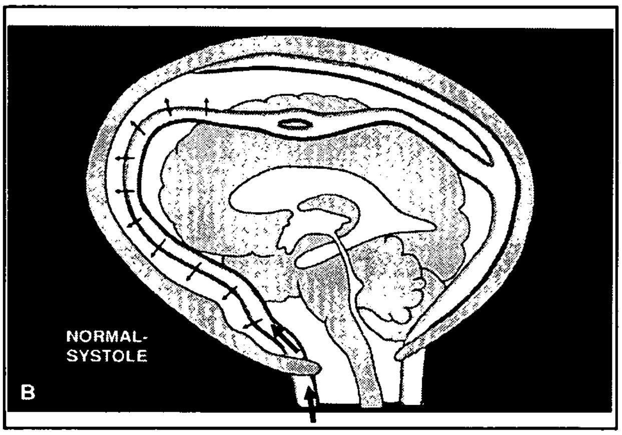
- In systole the expanding artery causes a volume conduction of CSF which compresses the outflow of the bridging veins

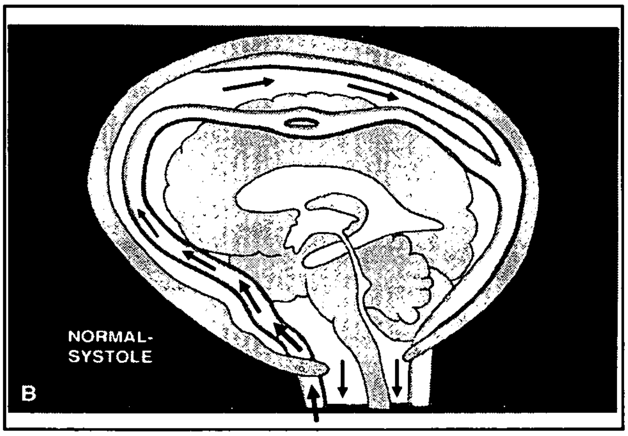


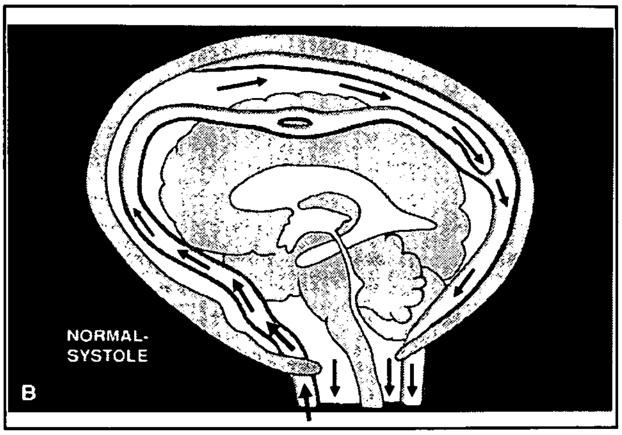
Normal compliance - Systole II

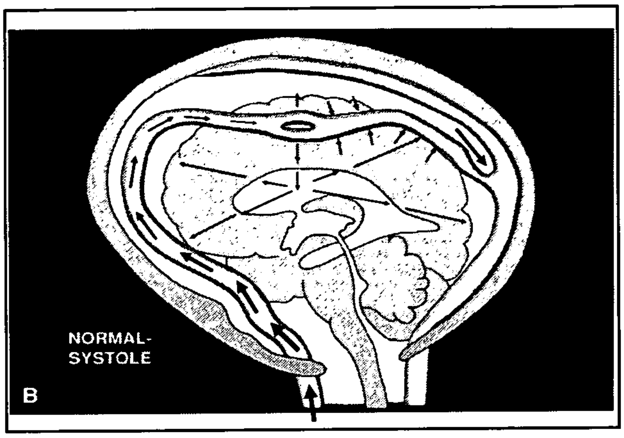
- At the same time CSF is propelled out of foramen magnum
- The damped arterial pulse pressure is then transmitted into brain

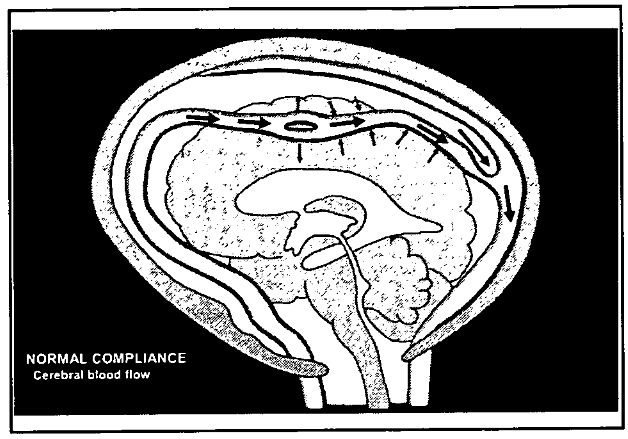






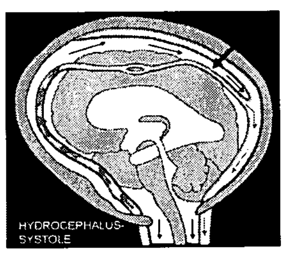






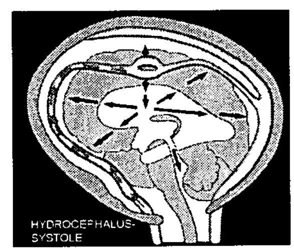
Decreased compliance - Hydrocephalus I

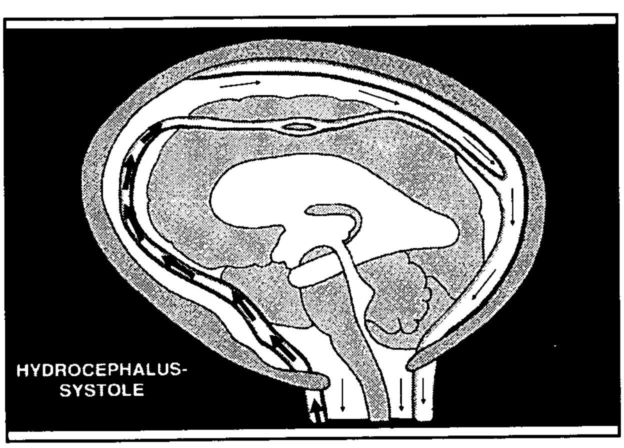
- In hydrocephalus the veins are compressed and the intracranial compliance is decreased
- The artery is unable to expand

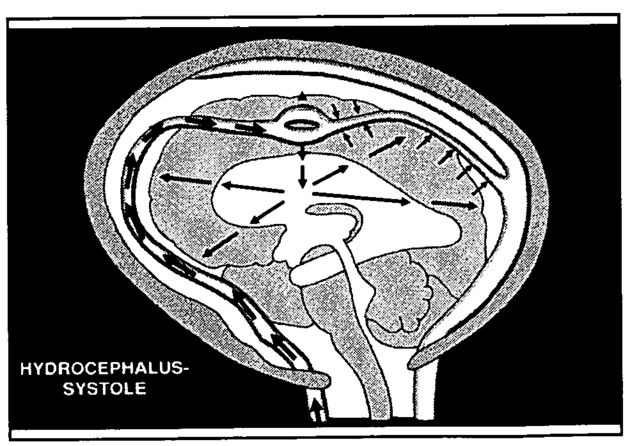


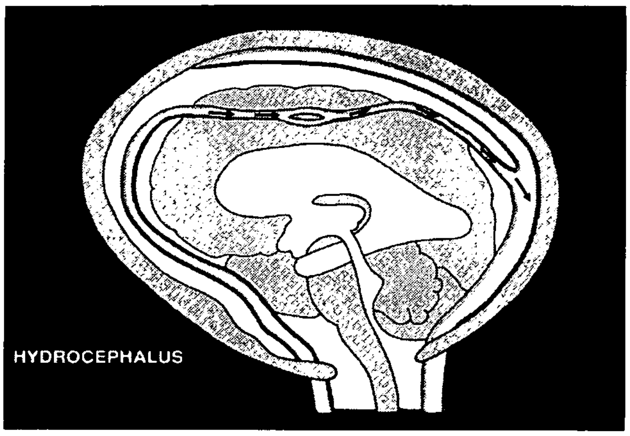
Decreased compliance - Hydrocephalus II

- The artery behaves like a rigid tube
- The pressure is transmitted <u>undamped</u> into the brain

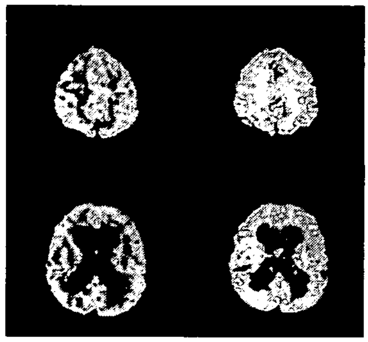








Cerebral blood flow in NPH



perfusion-weighted MRI

Before tap test After tap test

Hertel: 2003

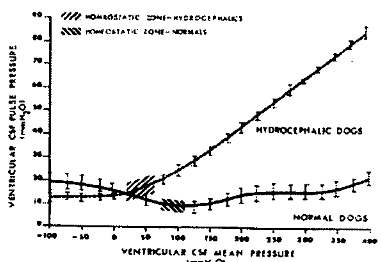
Evidence of decreased intracranial compliance in communicating hydrocephalus

1. Increased pulse pressure
2. Decreased pulse volume

Evidence of decreased intracranial compliance in communicating hydrocephalus

1. Increased pulse pressure
2. Decreased pulse volume

1. Increased CSF pulse pressure

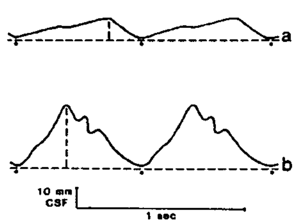


CSF infusion study in dogs

CSF pulse pressure as function of the mean CSF pressure: in normal and hydrocephalic dogs

Foltz EL: 1984

1. Increased CSF pulse pressure



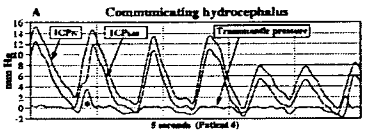
Normal controls
pp = 10 mm H_2O

Communicating HC
pp = 35 mm H_2O

The pulse pressure was significantly increased in dogs with communicating HC

Foltz EL: 1984

1. Increased CSF pulse pressure



PP = 12 mmHg

(normal PP is 2 mmHg)

The CSF pulse pressure was significantly increased in patients with NPH

Stephensen et al: Neurosurgery 2002

Di Rocco produced hydrocephalus in sheep by introducing a pulsating balloon into the lateral ventricle

Normal slit-like lateral ventricles

Communicating hydrocephalus

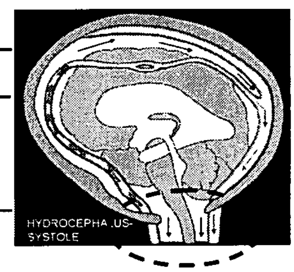
Di Rocco: 1978

Evidence of decreased intracranial compliance in communicating hydrocephalus

1. Increased pulse pressure
2. Decreased pulse volume

2. Decreased pulse volume

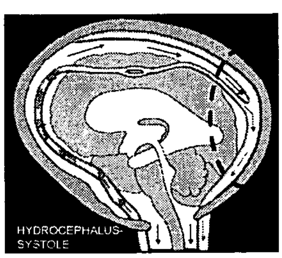
	For magnum pulse volume (ml/beat)
Normals	0.66
Hydrocephalus	0.34 *(P = 0.0006)*



D Greitz 1995

2. Decreased pulse volume

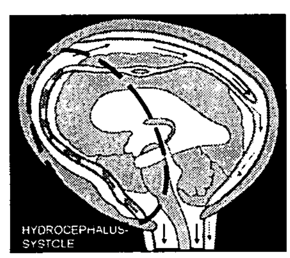
	Sag sinus pulse volume (ml/beat)
Normals	0.93
Hydrocephalus	0.67 *(P = 0.05)*



D Greitz 1995

2. Decreased pulse volume

	Arterial pulse volume (ml/beat)
Normals	1.33
Hydrocephalus	0.86 *(P = 0.002)*



Bateman: Neuroradiology 2005

Evidence of decreased compliance in normal-pressure hydrocephalus

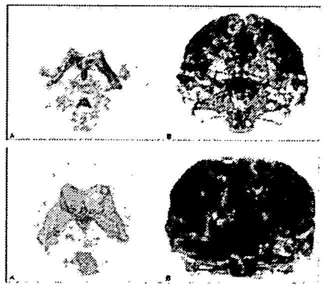
Nasel et al measured CSF motions in the SAS by using diffusion-weighted MRI

Nasel et al: Acta Radiol 2007

Three-dimensional CSF motion map (diffusion)

Controls

NPH



Restricted arterial pulsations decrease the CSF motions in SAS

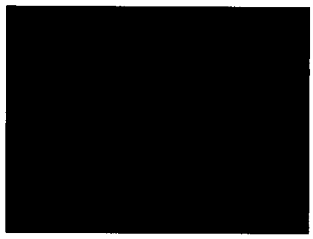
Nasel et al: Acta Radiol 2007

Evidence of decreased compliance in normal-pressure hydrocephalus

Ertl-Wagner et al used Cine MRI to examine the brain motions during a Valsalva maneuver

Ertl-Wagner et al: Eur Radiol 2001

Healthy volunteer before, during and after Valsalva



Normal compliance

Ertl-Wagner: Eur Radiol 2001

Normal-pressure HC before, during and after Valsalva

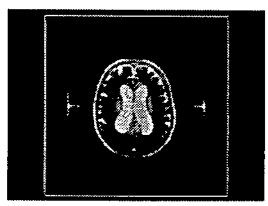
Decreased compliance

Ertl-Wagner: Eur Radiol

Healthy volunteer
normal compliance

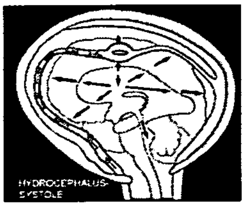
The volume of the ventricles decreased 18% during Valsalva

Normal-pressure HC
decreased compliance



The volume of ventricles decreased 0% during Valsalva

In summary:



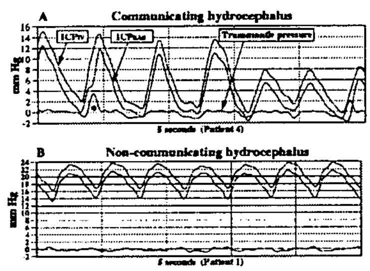
- Communicating hydrocephalus is caused by decreased intracranial compliance increasing the intracerebral pulse pressure

Major differences between the new and old concept

1. **CSF circulation**
2. **Hydrocephalus**
3. **New aspects of theory**

Is the hydrodynamic theory applicable on chronic obstructive hydrocephalus?

CSF pulse pressure in communicating HC and chronic obstructive HC



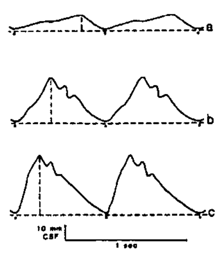
Communicating HC
pp = 8 - 12 mm Hg

Aqueductal stenosis
pp = 8 mm Hg

The CSF pulse pressure is increased in chronic obstructive HC

Stephensen: Neurosurgery 2002

CSF pulse pressure in communicating HC and chronic obstructive HC



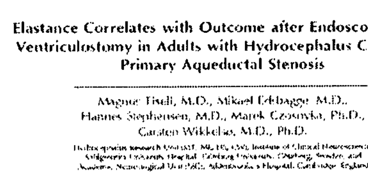
Normal

Communicating HC

Aqueductal stenosis

The CSF pulse pressure is increased in chronic obstructive HC

Foltz EL: 1984


Elastance Correlates with Outcome after Endoscopic Third Ventriculostomy in Adults with Hydrocephalus Caused by Primary Aqueductal Stenosis

Magnus Tisell, M.D., Mikael Edsbagge, M.D., Hannes Stephensen, M.D., Marek Czosnyka, Ph.D., Carsten Wikkelsø, M.D., Ph.D.

Tissel et al. found decreased intracranial compliance in patients with primary aqueductal stenosis

Tissel: Neurosurgery 2002

Is the hydrodynamic theory applicable on children with hydrocephalus?

Hydrodynamics and the fetus

Transvaginal Doppler during pregnancy

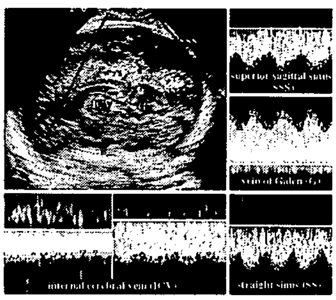


Figure 1. Intracranial venous circulation in the median section of fetal brain by transvaginal color Doppler image and physiologic venous-flow velocity waveform patterns of four different veins.

Pooh: Obstr and Gyn 1999

Transvaginal Doppler

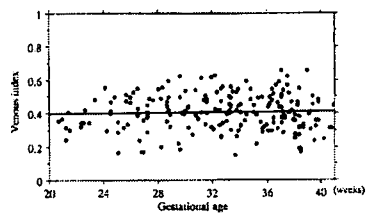
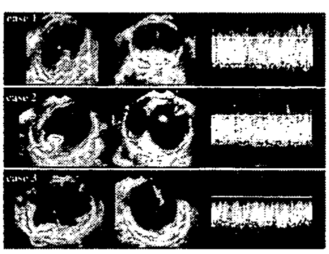


Figure 2. Venous index of the superior sagittal sinus between 20 and 40 weeks' gestation.

Venous pulsatility index of superior sagittal sinus during pregnancy

Pooh: Obstr and Gyn 1999

Transvaginal Doppler: 3 different cases of hydrocephalus



Abolished venous pulsations in the superior sagittal sinus indicating decreased compliance in fetal hydrocephalus

Pooh: Obstr and Gyn 1999

It is suggested that:

1. Chronic obstructive hydrocephalus and
2. Chronic hydrocephalus in infants -

also are caused by decreased intracranial compliance