Pediatric hydrocephalus

proceeding beyond Dandy and Blackfan

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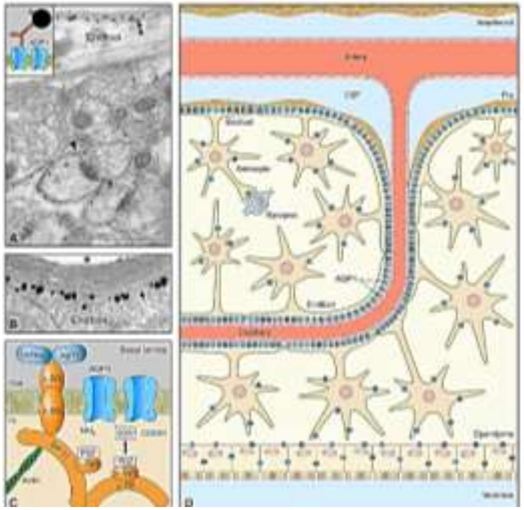
History of concepts

- Dandy and Blackfan1914: global bulk flow model
  - CSF secreted by choroid plexuses, absorbed by meninges
  - obstructive & communicating hydrocephalus
- Bering 1952, 1954: free diffusion of heavy water between CSF/ISF/blood
- Bering 1955, 1962; Pettorossi & Di Rocco 1978: pumping effect of systolic stroke, concept of compliance
- Agre 1993 (Nobel Prize 2003): water transporters aquaporins

Aquaporins in the CNS



Nagelhus & Ottersen 2013

- AQP1: choroid plexus
- AQP4: → water transported across brain surfaces & into vessels, either way
  - ependyma
  - subependymal, subpial, peri-capillary astrocytic endfeet
  - depends on pressure & osmolarity gradients
  - little known about regulation, GABA likely involved
- Both transport water only, not even ions
  - CSF tracers experiments useless

Li et al 2015

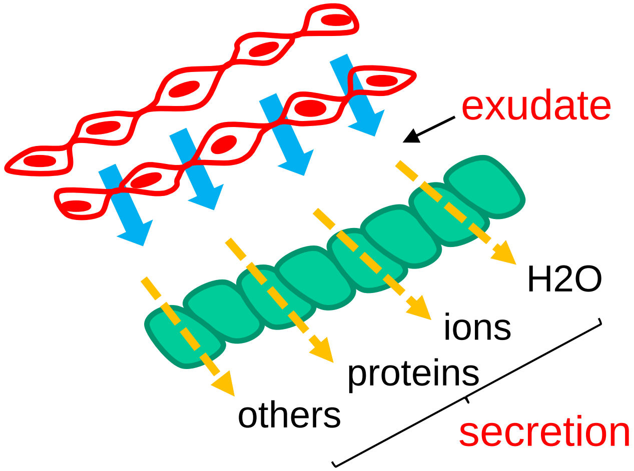
Cranio-spinal CSF

- CSF volumes larger than previously thought
  - ventricles 25 ml (10 ml in neonate [Xenos et al 2002])
  - extracerebral, intracranial: 230-270 ml [Lüders 2002]
  - spinal 150 ml
- Significance of peri-cerebral spaces [Rekate et al 2008]
  - ventricles may enlarge without compressing the parenchyma
    - but not beyond without destruction, once peripheral spaces are filled
- Hydrocephalus = fluid transfer from periphery to ventricles, tissue loss develops late

Definition of flows

- Bulk flow: net motion of a volume of fluid between two points
- Oscillatory flow: to and fro displacement of a volume of fluid
- Diffusion: Brownian motion of individual molecules within a fluid
- Cilia-directed near-wall flow
  - likely significant for molecular transport toward targets
  - causally associated with rodents' hydrocephalus, probably not humans'

CSF secretion by choroid plexus



Permanent but variable, regulated, two steps

1. Passive exudate: artery → interstitium
   - perfusion pressure Pa, Pv, pCO2, ICP
     - arterial innervation: sympathetic ↓, cholinergic ↑
     - humoral: norepinephrin, angiotensin II, serotonin
2. Active secretion: interstitium → ventricle, regulated
   - water: AQP1 (↓ atrial natriuretic peptide ANP; ↑ arginine vasopressin AVP)
   - ions: ATP hydrolysis (carbonic anhydrase)
   - secretome: regional targets, evolving with maturation

Yasuda et al 2002; Galarza 2002; Potokar et al 2016;Lun et al 2015

Ependymal/astrocytic absorption (ventricular)

- Abundant evidence of ventricular absorption of CSF
  1. clinical: chronic untreated obstructive hydrocephalus
  2. experimental: dilatation after ventricular obstruction develops late
  3. histological: ependymal & astrocytic AQP4
  4. functional: secretome matches receptors of ventricular walls
     - signaling & neurotrophic molecules to subventricular progenitors
- Across ependyma CSF → ISF → veins

Bulat & Klarica 2011; Lun et al 2015

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- Across ependyma
  - CSF → ISF → cerebral veins

    → subpial/VRS → arachnoid → dural veins

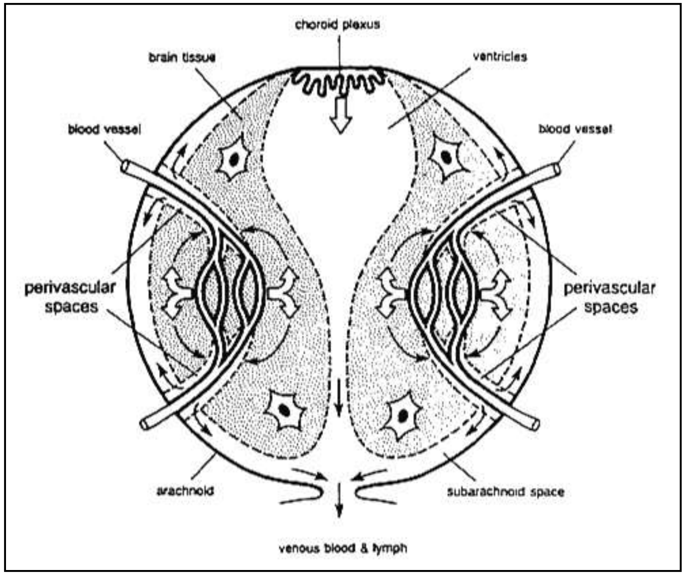
Bulat & Klarica 2011; Lun et al 2015

Extra-ventricular CSF production (brain surface)

- Clinical evidence
  - choroid plexectomy: CSF production maintained
  - extracerebral CSF present in obstructive hydrocephalus
- Histological evidence: subpial astrocytic endfeet rich in AQP4 channels
- Anatomical supporting data
  - from subpial to Virchow Robin (VRS) to perivascular spaces (PVS)
    - around arterial & venous perforators
    - lymphatic-like dainage of interstitial fluid

Zhu & Di Rocco 2013; Cserr et al. 1992

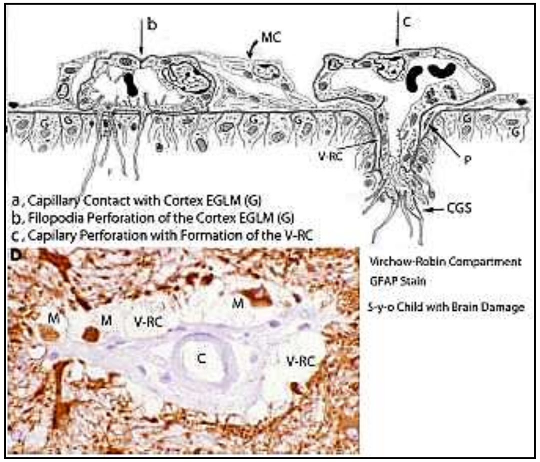
Perivascular and Virchow-Robin spaces



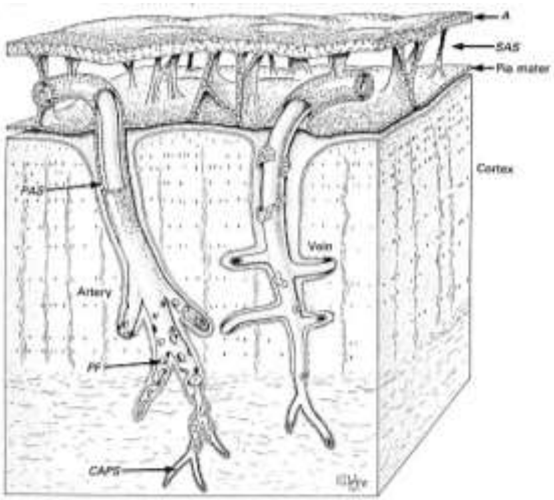
Cserr et al 1992

- Subpial space
- PVS = between arachnoid and vessels
- VRS: PVS + subpial

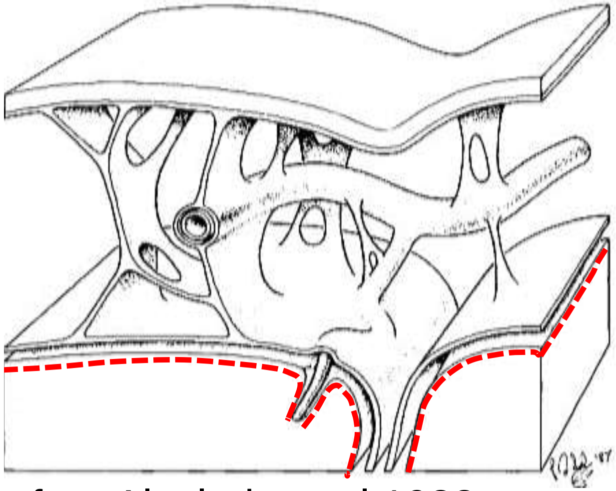
- Water transportation: ISF to astrocytic endfeet (AQP4) → subpial & VRS → PVS



Marin-Padilla 2012

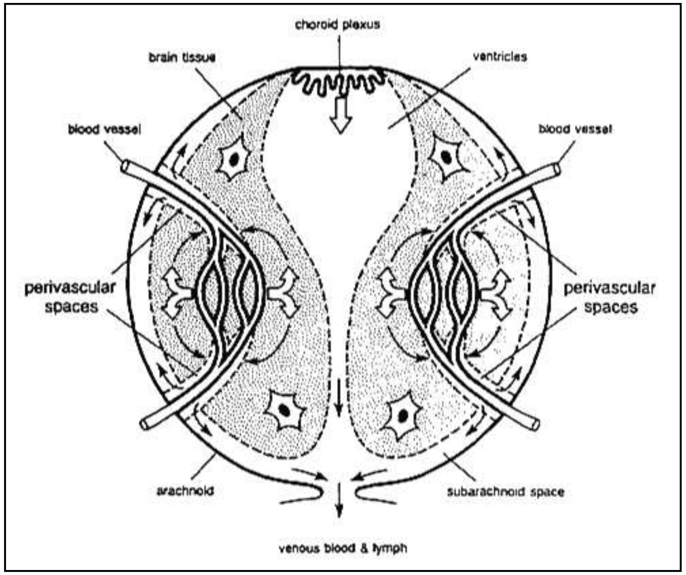


Zhang et al 1990



after: Alcolado et al 1988

Perivascular and Virchow-Robin spaces



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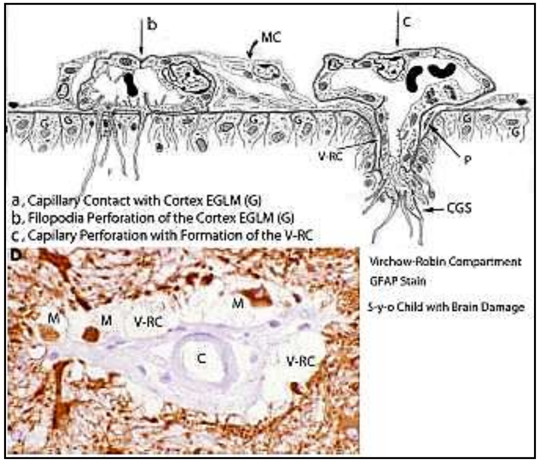

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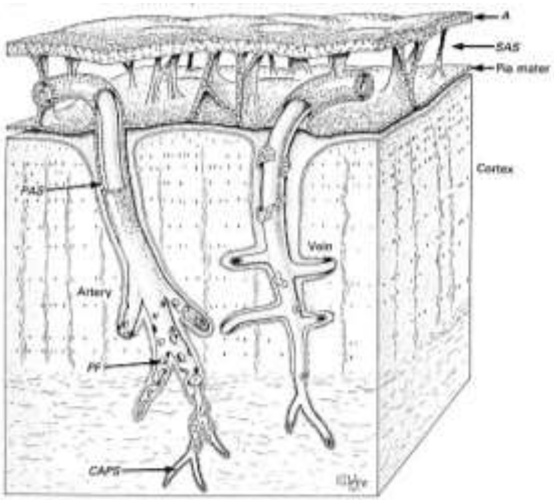

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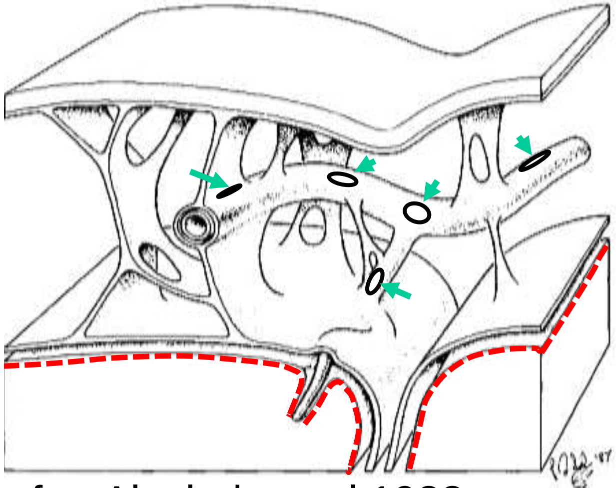


after Alcolado et al 1988

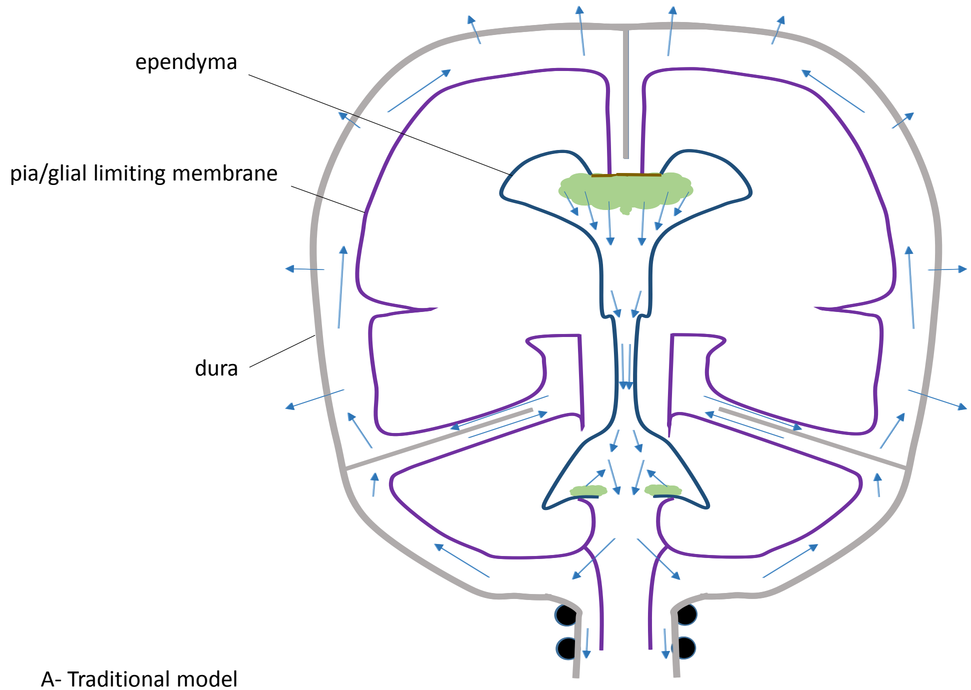
Dural and parenchymal CSF absorption

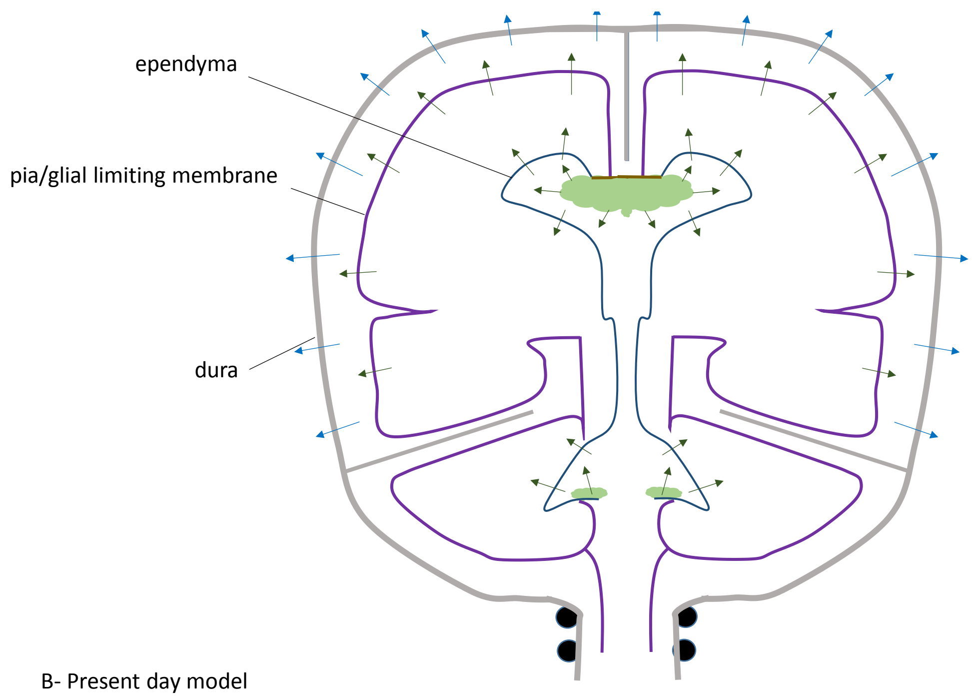
- Absorption equals production, ↑ with ICP
- Multiple absorption sites available, no known hierarchy
  1. Passive: arachnoid granulations, dural clefts to dural sinuses
  2. Passive: cranial/spinal nerve sheaths to extra-dural lymphatics
  3. Active: AQP4 ependyma, subpial/VRS astrocytic endfeet
     - CSF_{vent} ↔ interstitial fluid ↔ $CSF_{extravent}$

       ↕

       capillaries
- Produced and absorbed by brain surfaces, CSF may be transported across the brain

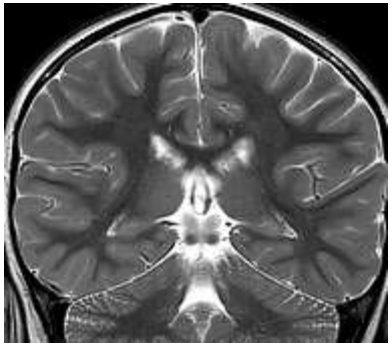
Koh et al 2005; Pollay 2010; Bulat et al 2008; Papadopoulos & Verkman 2012

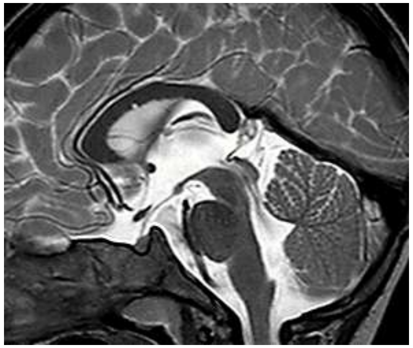




Not one, but multiple transverse bulk flows

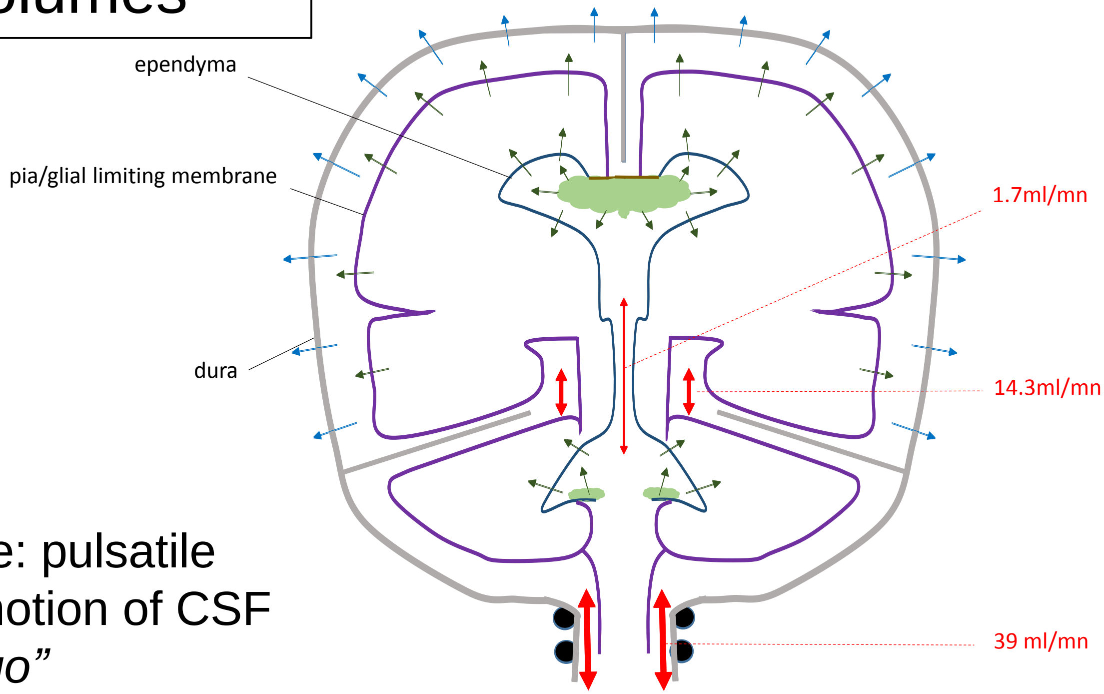
One bulk flow would mean pressure higher in ventricles than in cisterns than on the convexity





Pressure actually higher in cisterns than in 3rd ventricle and over convexities than in lateral ventricles

Pulsating CSF volumes



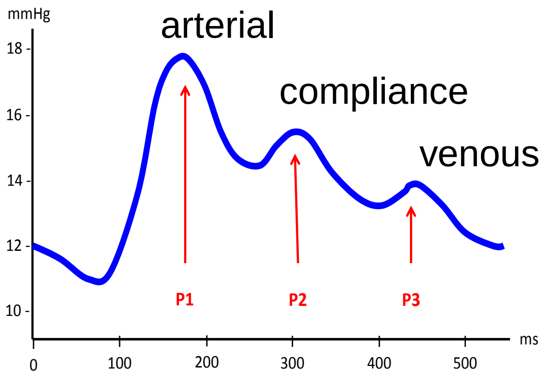
Major hydrodynamic force: pulsatile systolic force = oscillatory motion of CSF not the *"vis a tergo"*

	Location	Volumes	Percent
Systolic influx	head	650 ml/min	100%
blood	vessels	611 ml/min	94%
CSF	C2-C3	39 ml/min	6%
	incisura	14.3 ml/min	2.23%
	aqueduct	1.7 ml/min	0.26%
	absorption	0.35 ml/min	0.05%

Enzmann and Pelc 1993

Systolic pressure curve and hydrocephalus

- *Pressure* everywhere the same in closed cranium
- But pulsatile force transmitted, and resisted (impedance/compliance) by visco-elastic brain, theca, vascular tree
- *Force* gradients develop at each arterial stroke
- Normal: P1 > P2 > P3



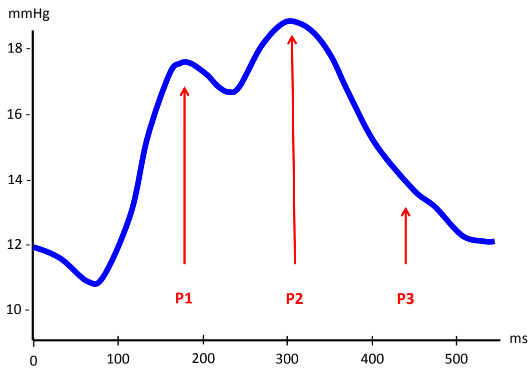


Fig 03 b

Systolic pressure curve and hydrocephalus

- Decrease compliance: P2 > P1 > P3
- If ventricular obstruction, P2 increased in ventricles, but not outside: the ventricle dilates
- By effacing the pericerebral spaces, ventricular dilatation *redirects the pulsatility to the ventricle*, so re-inforcing P2

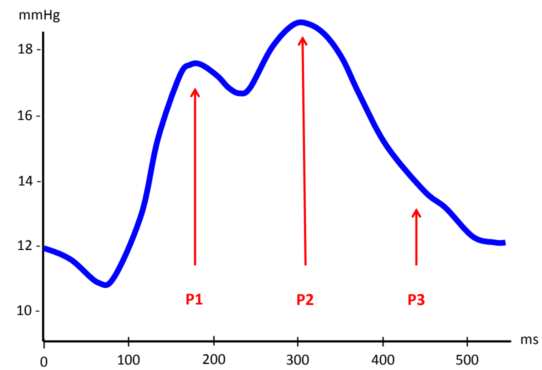


Fig 03 b

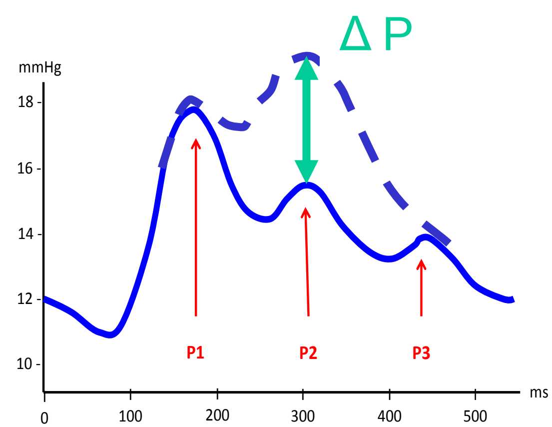
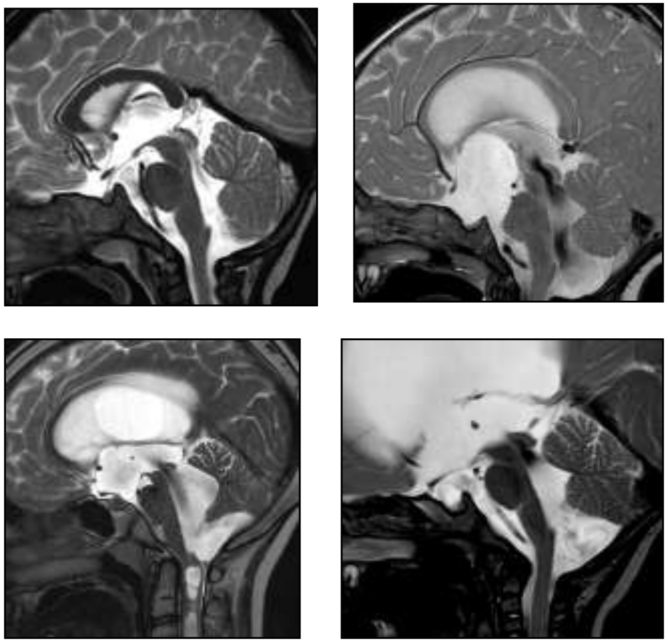


Fig 03 a

Systolic pressure curve and flow void

- The redirected medial-ward pulsatility re-inforces P2
- This is reflected by the amplitude of the flow voids
- May also be re-inforced by the decreased compliance (rebound effect)



Hydrocephalus: one morphology, different mechanisms

- Two groups, anatomically distinct
  1. obstructive, ventricular or cisternal
  2. non-obstructive
- Two processes,
  1. compliance failure
  2. absorption failure
- Acting singly (low ICP) or in association (high ICP)

Hydrocephalus: one morphology, different mechanisms

- Four combinations
  1. obstructive (normal absorption) = low pressure
     - e.g., chronic aqueductal stenosis
  2. obstructive + poor absorption= high pressure
     - e.g., midline tumor, infection
  3. absorptive (normal compliance) = low pressure
     - e.g., benign external hydrocephalus
  4. absorptive + low compliance = high pressure
     - e.g., choroid plexus papilloma

Restoration (or lack of) of the cerebral mantle

1. Parenchymal effects of hydrocephalus: age, duration
2. Parenchymal effects of causal pathology
3. Intrinsic parenchymal response

Factors related to age/stage of development

- In young patients, ventricular dilation compensated by macrocephaly: brain parenchyma stretched but preserved
- Connectivity about term still incomplete, axonal guidance still there, potential for further / restored growth
- In early brain, myelin = most potent inhibitor of axonal development
  - myelin associated inhibitors or MAIs
  - no myelination before term, remains partial for months

Bonfanti, Prog Neurobiol 2006; Fancy et al, Ann Rev Neurosc 2011;
Akbik et al, Exp Neurol 2012

Recents concepts regarding pediatric hydrocephalus

- Not a single longitudinal, but multiple transverse bulk flows (parenchymal absorption/production of CSF)
- Systolic pulsatile force against visco-elastic vessels, brain, theca (compliance)
- Hydrocephalic ventriculomegaly redirects the pulsatile force medially
- Compliance loss and secretion/absorption mismatch are different processes
  - low pressure hydrocephalus when occur singly
  - high pressure hydrocephalus when associated
- Factors of parenchymal recovery not really studied yet