Age-induced increase in the energy transmitted towards the cerebral circulation as a contributor to impaired brain function

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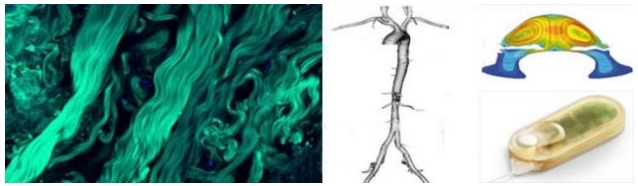


Cognition and Age

Continuous decline in cognitive skills with age

Increasingly aged population → cognitive impairement becomes a major health issue

Associated with high aortic stiffness (c-f PWV)

- independent predictor of cardiovascular and **cerebrovascular diseases**

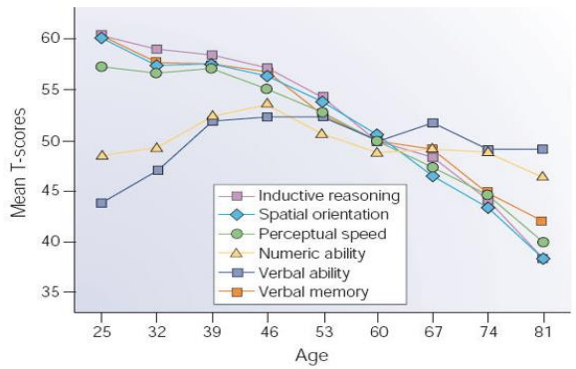


Figure. Cognitive decline with age (*Hedden et al.)*

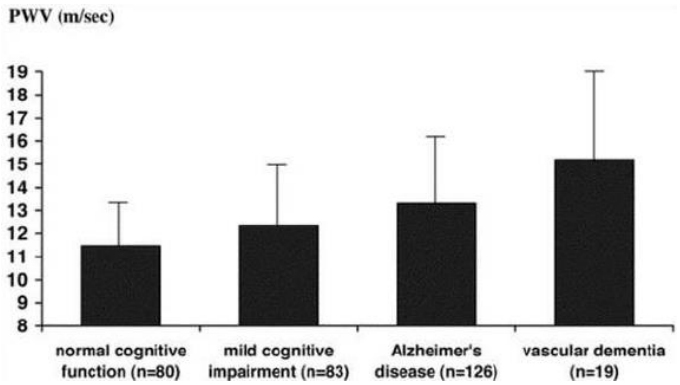


Figure. PWV and cognitive impairment *(Singer et al.)*

Hedden et al. (2004) *Nature Reviews Neuroscience* volume 5, pages 87–96.

Singer et al. (2014) *Ageing Research Reviews*, 15, 16-27.

What is the pathophysiological mechanism linking high aortic stiffness and cognitive impairment?

Effect of ageing on arterial stiffness

Non-uniform stiffening of arterial tree:

- Proximal aorta becomes stiff
- Periphery is not significantly affected

Impedance mismatch reduced

Forward pressure wave amplitude increase

What is the pathophysiological mechanism linking high aortic stiffness and cognitive impairment?

Prevalent theory

Transmission of excessive pulsatile energy towards the brain because of decrease in impedance mismatch

Tested *in vivo* by Mitchell et al.

- Quantified carotid pulsatility index:
  (Flow Pulse Amplitude) / (Mean Flow)
- Correlation with brain damage

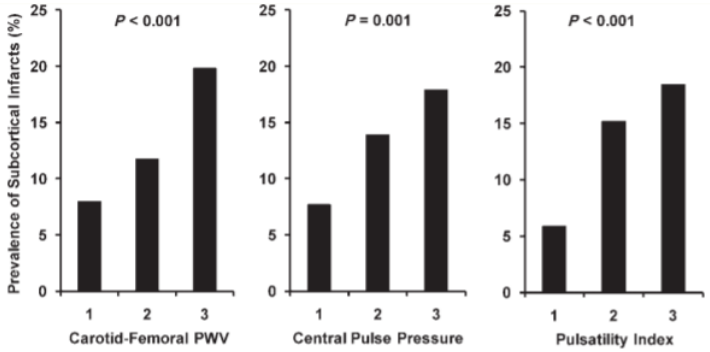


Figure. Prevalence of subcortical infarcts and pulsatility in the carotid *(Mitchell et al.)*

Mitchell et al. (2011) *Brain. 134(11): 3398–3407.*

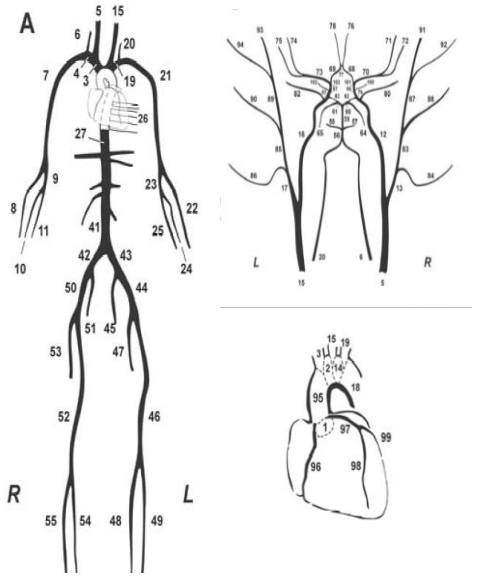
Major challenges

- Inherent difficulty in investigating wave transmission *in vivo*
- Need of simultaneous measurements of blood flow and pressure in cerebral arteries
- Impossible to employ wave analysis techniques

Mathematical modeling could be a valuable tool to investigate the pathophysiological link

Previous work from our laboratory

1-D model of the systemic circulation



Continuity

$$\frac{\partial A}{\partial t} + \frac{\partial Q}{\partial x} = 0$$

Momentum

$$\frac{\partial Q}{\partial t} + \frac{\partial}{\partial x}\left(\int_A u^2 dA\right) = -\frac{A}{\rho}\frac{dP}{dx} - 2\pi R \frac{\mu}{\rho}\frac{\partial u}{\partial r}\bigg|_{r=R}$$

Constitutive equation

$$A(t) = A^e\big(P(t)\big) + A^v(t)$$

→ Previously validated *in vivo*

Adapted to incorporate effects of ageing

- ✓ Non-uniform stiffening of arterial tree
- ✓ Increase in LV contractility

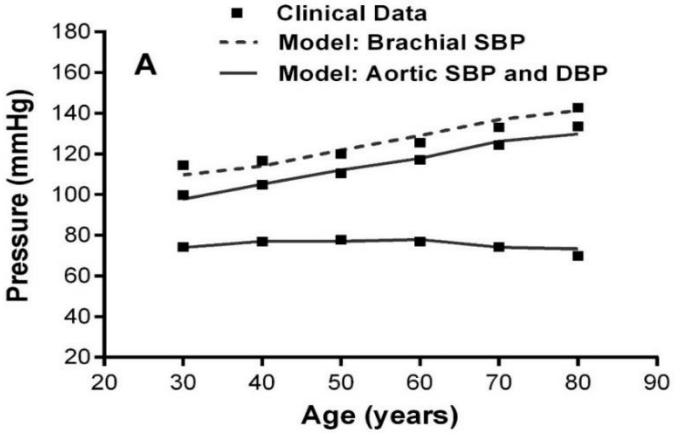


Figure. Pressure evolution predicted by the ageing model vs clinical data (*Pagoulatou et al.*)

Reymond et al. (2009). *Am J Physiol Heart Circ Physiol.*
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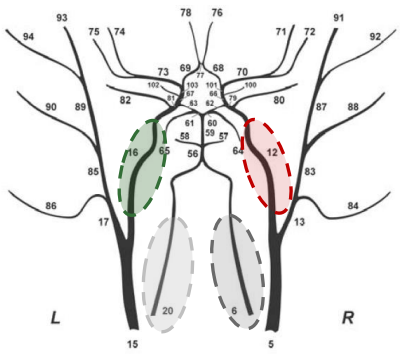
Pagoulatou et al. (2017). *PLoS ONE* 12(7): e0182173

Our Approach

Investigate the age-induced evolution of energy transmission towards the cerebral circulation using the **ageing model** and novel **wave power analysis.**

1 Isolated pressure and flow curves of ageing model at the **Ascending Aorta** (**AA**) and the 4 feeding vessels of cerebral circulation :

- **Right** & **Left Internal Carotid Artery** (**ICR** & **ICL**)
- **Right** & **Left Vertebral Artery** (**VR** & **VL**)



2 Employed the wave power analysis by Mynard et al.

- Calculated wave power:

$$d\pi = dPdQ$$

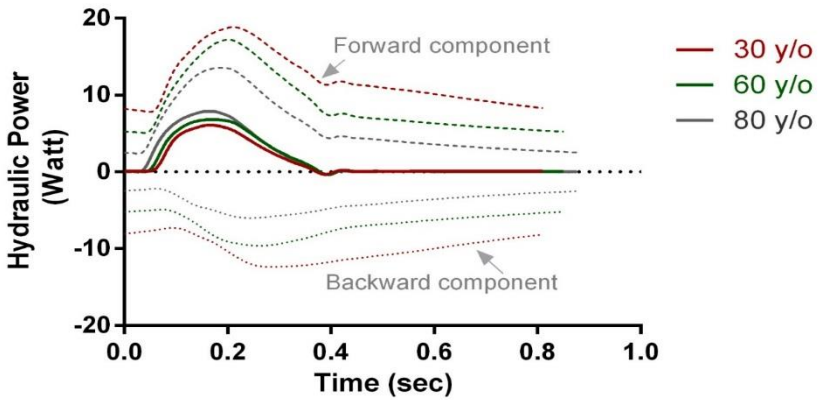
- Hydraulic power:

$$\Pi = \Pi_P + \Pi_Q = PQ + \frac{\rho Q^3}{2A^2}$$

- Separated hydraulic power into forward, backward and interaction terms:

$$\Pi = (\Pi_{P+} + \Pi_{Q+}) + (\Pi_{P-} + \Pi_{Q-}) + \Pi_X$$

Hydraulic power in the AA

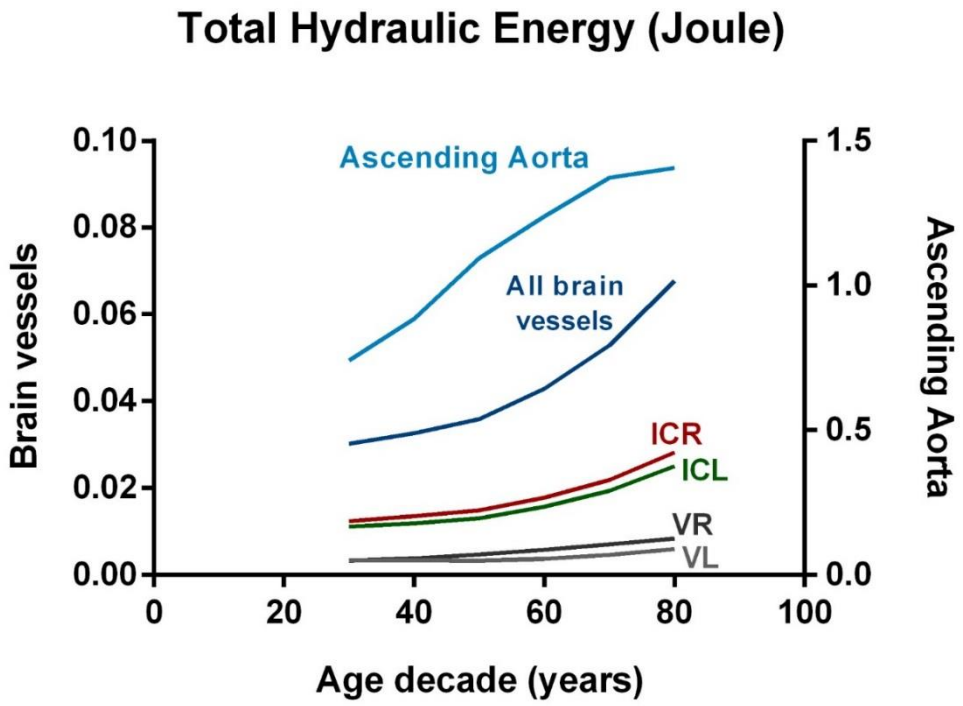


Mynard et al. (2016). *Am J Physiol. Heart Circ Physiol.* Volume 310, issue 8.

Total Hydraulic Energy

Integration of power curves, after subtraction of the offset (energy potential):

$Total\ HE$ = *(Forward HE – offset) + (Backward HE – offset) + (Interaction term)*



How much of this energy is due to the early systolic forward compression wave (FCW)?

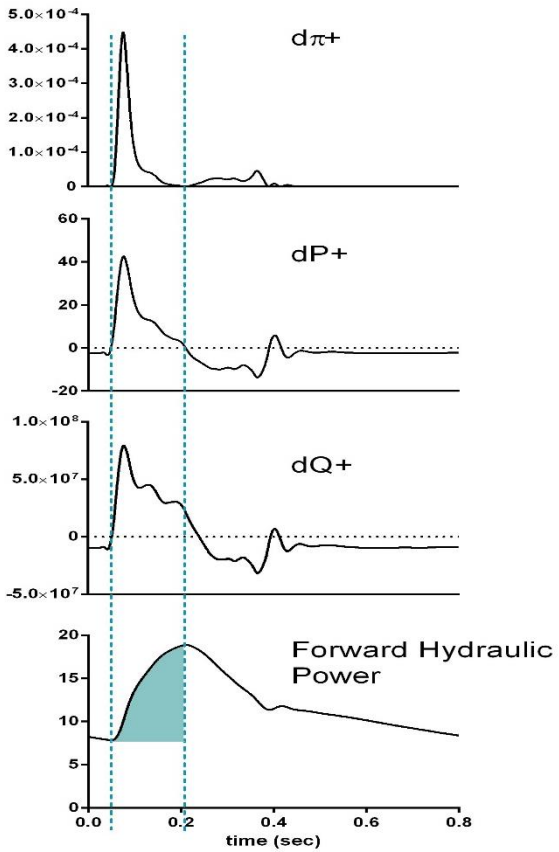
Why the early systolic FCW?

- ✓ Cancel out the effect of reflections travelling up from the distal aorta towards the brain

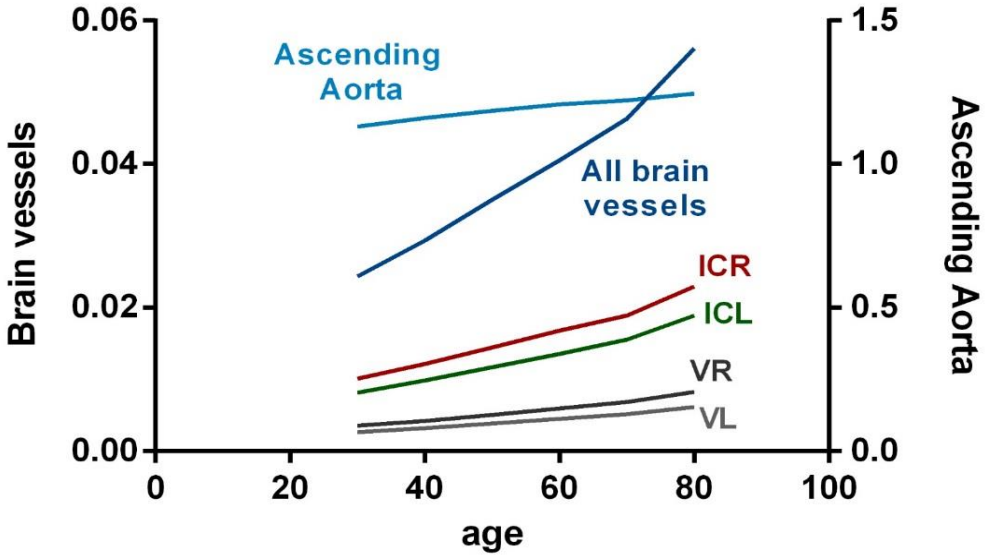
How to calculate HE carried by FCW?

- ✓ Isolated the timing of the FCW
- ✓ Integrated the hydraulic power curve over this timing

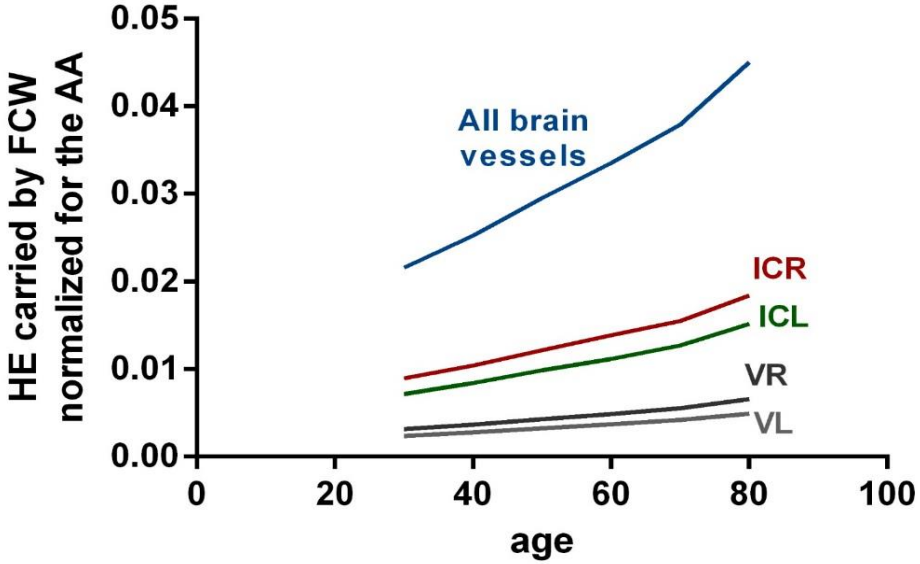
Timing of the FCW in the AA



Hydraulic Energy (Joule) carried by FCW



… In relative terms



Take home message

Results support original hypothesis

Age-related arterial stiffening leads to an increase in the transmission of hydraulic energy carried by early systolic forward wave towards brain, which might compromise its function and structure

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