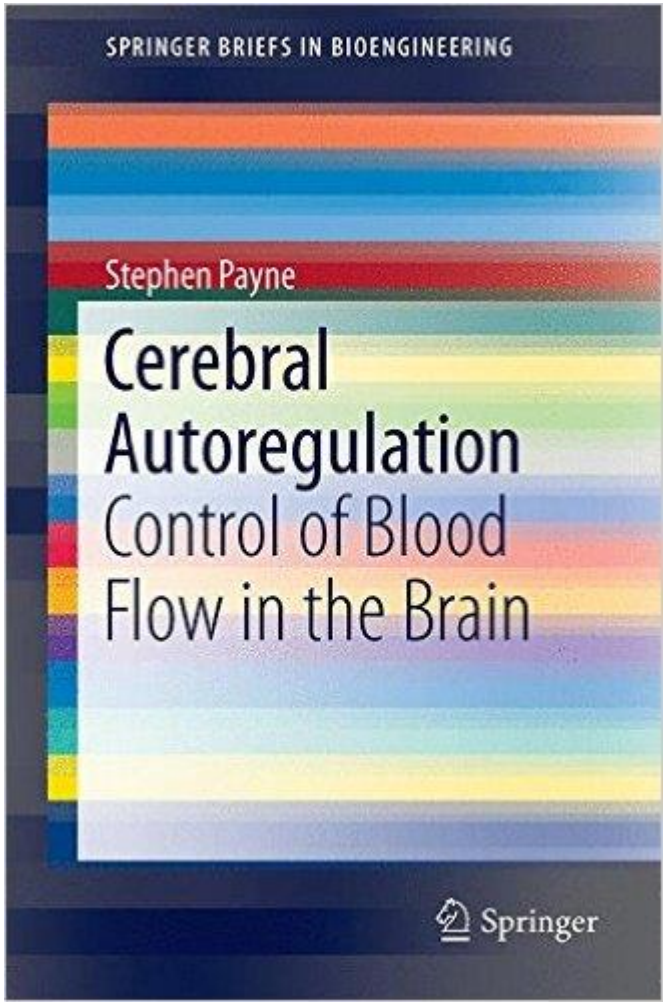
Control of cerebral blood flow perfusion

Stephen Payne
Institute of Biomedical Engineering
University of Oxford

Overview

1. Introduction
2. Physiological basis
3. Measurement techniques
4. Models
5. Analysis
6. Clinical practice
7. Conclusions



1. INTRODUCTION

Introduction

- Brain is 12-15 % of body's cardiac output and 20 % of oxygen consumption
- Metabolic requirements largely static
- Brain one of most tightly regulated body organs
- CBF regulated over wide range of ABP
  - Cerebral autoregulation

Autoregulation: The Lassen curve

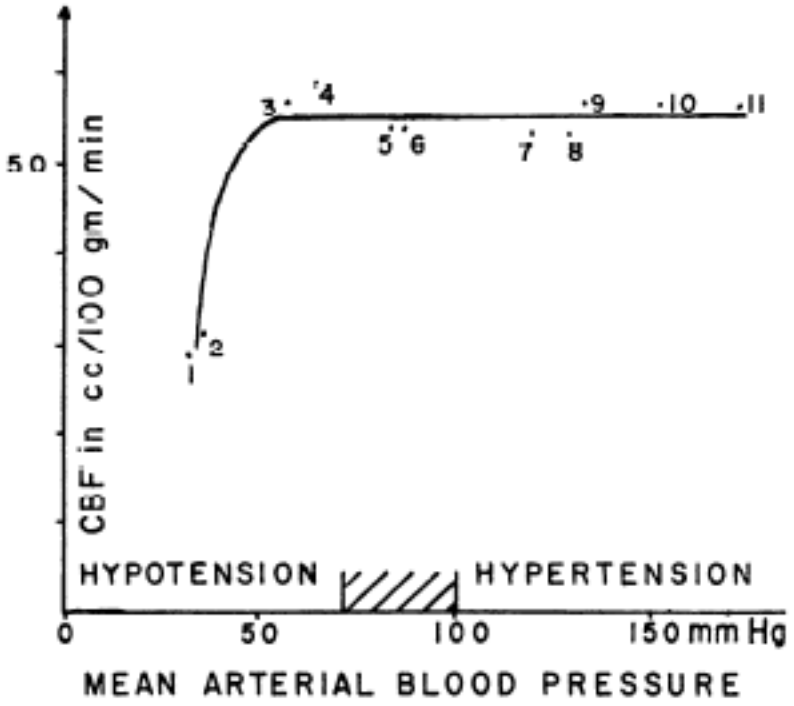


FIG. 1. Cerebral blood flow and blood pressure. Mean values of 11 groups of subjects reported in 7 studies have been plotted. Various acute and chronic conditions have been selected, characterized by a change in blood pressure. In all, this figure is based on 376 individual determinations.

1 and *2*, Drug-induced severe hypotension (81). *3* and *4*, Drug-induced moderate hypotension (206). *5* and *6*, Normal pregnant women and normal young men (206, 173). *7*, Drug-induced hypertension (230). *8*, Hypertensive toxemic pregnancy (206). *9*, *10*, *11*, Essential hypertension (229, 131, 228).

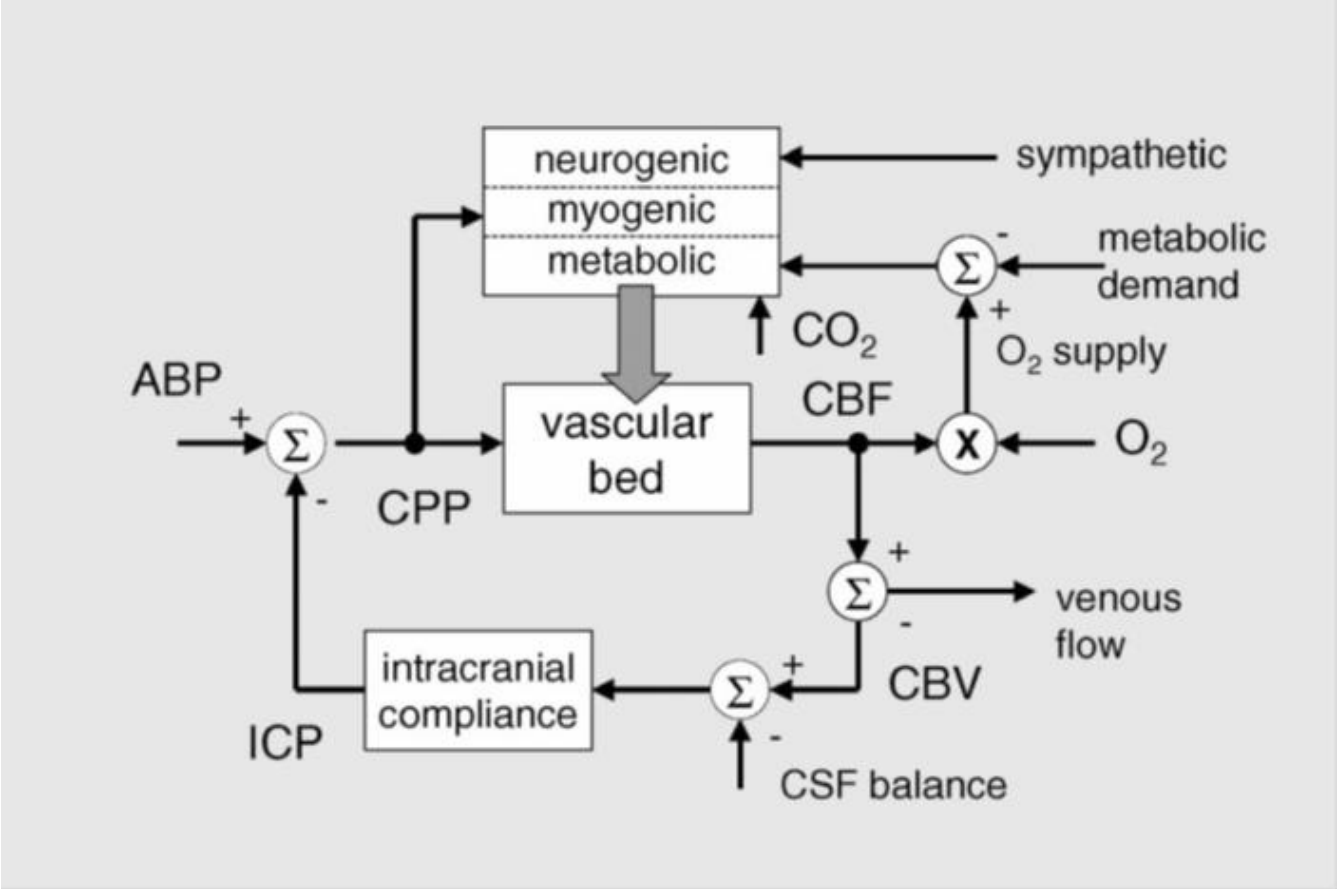
Lassen, Phys Rev, 1959

The Lassen curve: Comments

- 11 selective measurements from 9 studies
- Very flat CBF over wide range of ABP
- Lower (but no upper) limit of autoregulation

- Previously, CBF thought to vary linearly with ABP (with influence of blood gas levels)

Physiological basis



Panerai, Cardiovasc Eng, 2004

Physiological basis

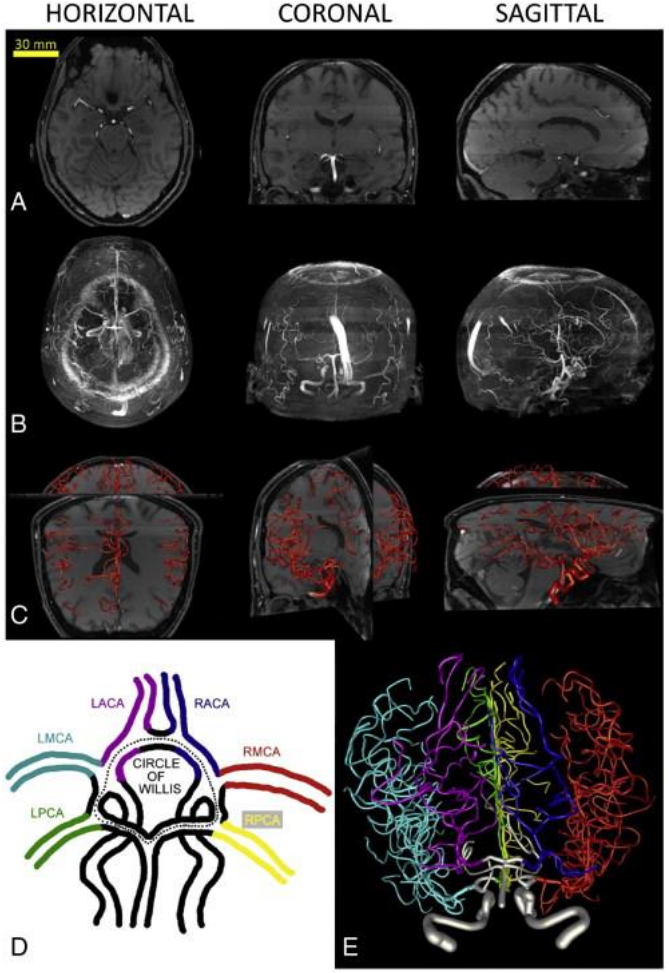
- Note multiple factors
- Note control of both CBF and CBV
- CBF governed by Central Perfusion Pressure (ABP-ICP)

- Local versus global control mechanisms
- Static versus dynamic control

2. PHYSIOLOGICAL BASIS

Cerebral vasculature

- Highly complex, structurally heterogeneous, inter-connected network of blood vessels



Wright et al., Neuroimage, 2013

Variations

Table 1: Classification of the variations of the CW, significant during uSCP

Type	Variation	Zone at risk of hypoperfusion	Frequency
Type IA	Left PComA	Left middle cerebral artery	35.6% (178/500)
Type IB	AComA	Left anterior cerebral artery	2% (10/500)
Type IIA	Left PComA + AComA	Left anterior cerebral artery + left middle cerebral artery	4.8% (24/500)
Type IIB	Left P1 or right VA	Left middle cerebral artery + left posterior cerebral artery	9.2% (46/500)
Type IIIA	Right A1	Right anterior cerebral artery + left anterior cerebral artery + left middle cerebral artery	6% (30/500)
Type IIIB	AcomA + right VA	Left anterior cerebral artery + left middle cerebral artery + left posterior cerebral artery	0.2% (1/500)
Type IV	Right A1 + right VA or right A1 + left P1	Right anterior cerebral artery + left anterior cerebral artery + left middle cerebral artery + left posterior cerebral artery	0.8% (4/500)
Total			58.6% (293/500)

Showing affected vessels, vessel basins at risk of hypoperfusion and frequency of each variations type for this study. PComA: posterior communicating artery; AComA: anterior communicating artery; VA: vertebral artery; uSCP: unilateral selective cerebral perfusion.

Papantchev et al., E J C-T Surg, 2013

Haemodynamics

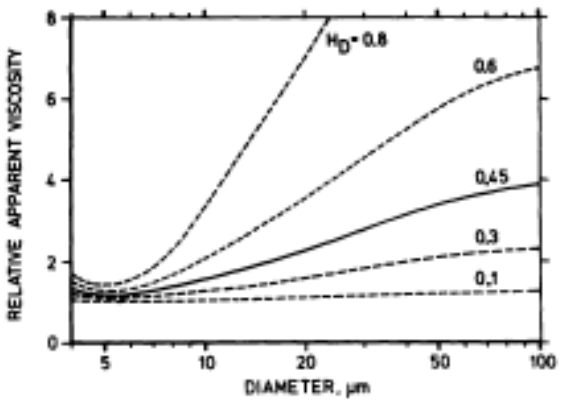
- Poiseuille equation:

$$Q = \frac{\Delta P}{R}$$

- Vessel resistance:

$$R = \frac{8\mu L}{\pi r^4}$$

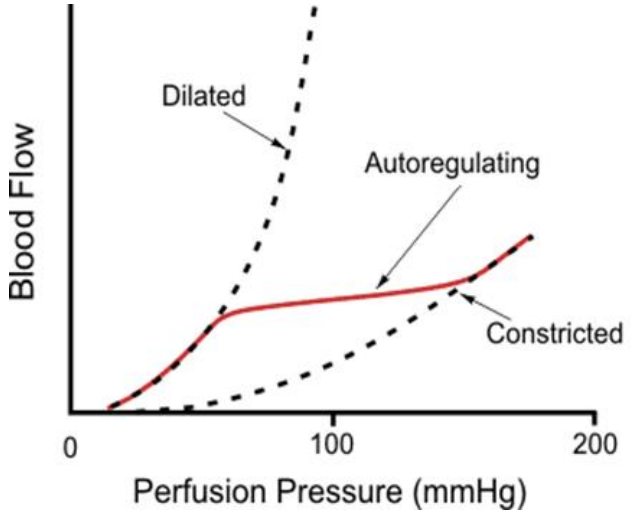
- Viscosity dependent upon diameter and haematocrit:



Pries et al., CircRes, 1990

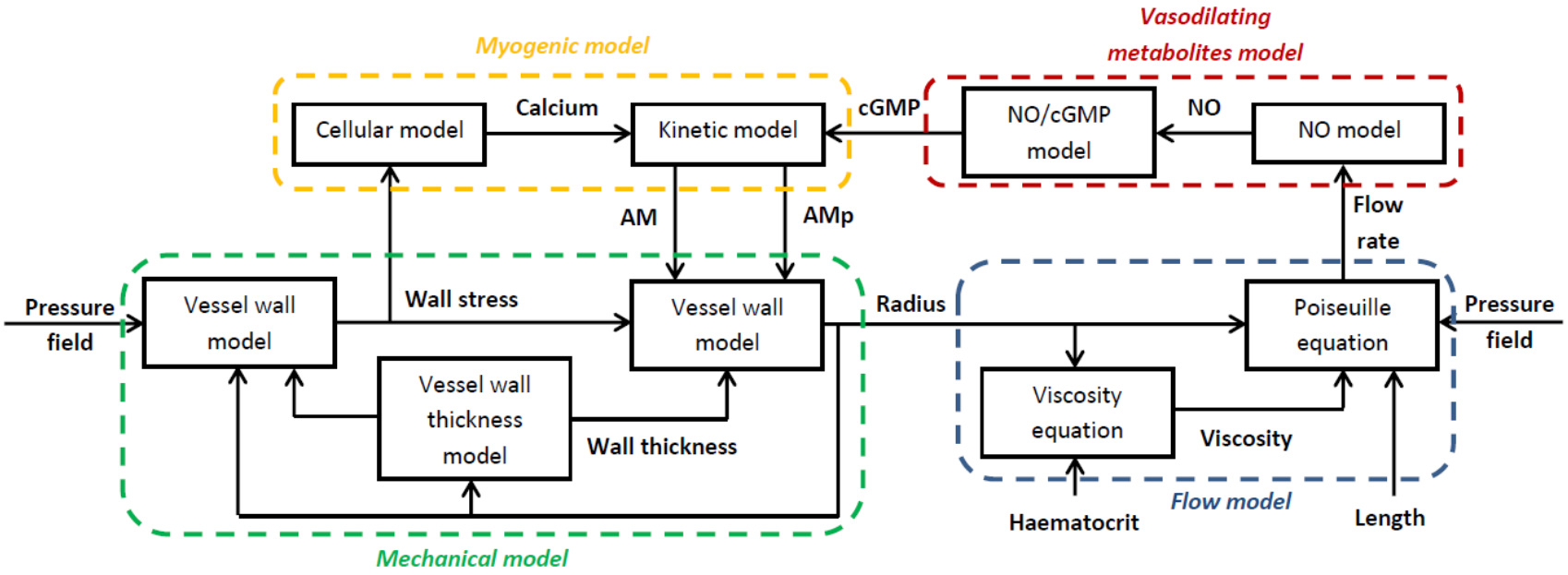
Regulation of flow

- Resistance only dependent upon radius, so blood flow only controlled by changes in radius:
  - Very sensitive to radius
- Different vessel generations respond with different sensitivities
  - Very finely controlled



Flow regulation pathways

- Key substances involved are:
  - Intracellular calcium
  - Nitric Oxide



Effects of blood gas levels

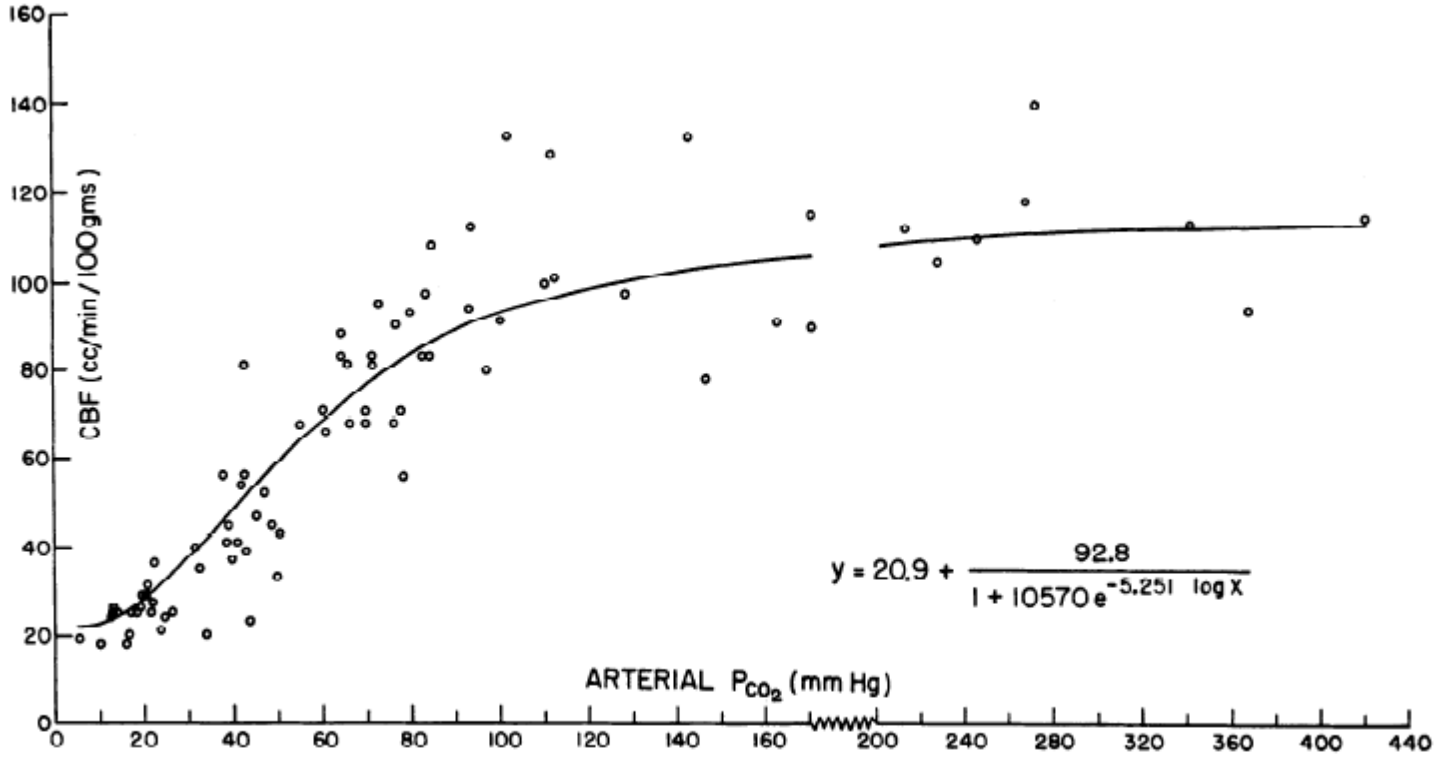
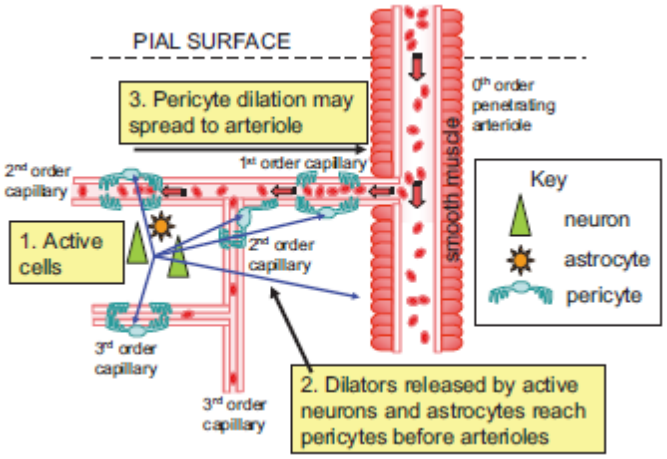


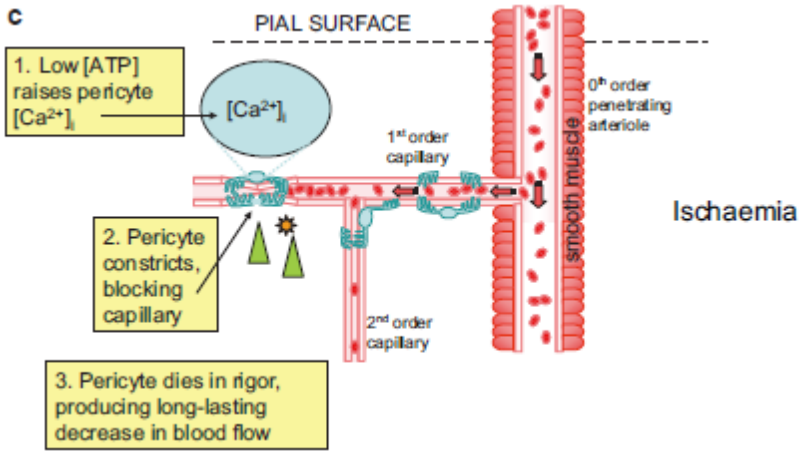
FIG. 3. Curve and its equation describing relationship between cerebral blood flow (*CBF*) and arterial Pco_2 where y = *CBF* and x = Pco_2. o = Individual data points for each of the eight monkeys.

Reivich, AJP, 1964

Pericytes

- Capillary level control through pericytes
  - These act before arteriolar dilation
  - Balance between two / driver or driven

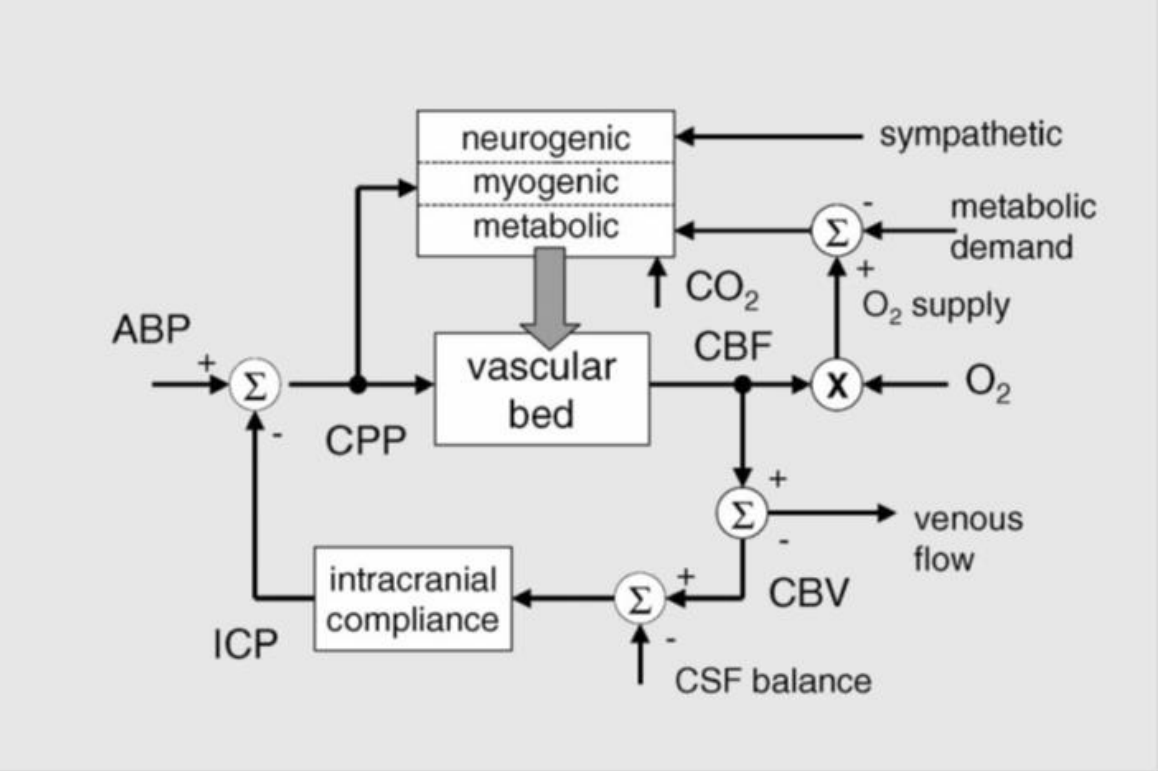




Hall et al., Nature, 2014

Sympathetic activity

- Least well understood component
  - Override or centralised control?



Panerai, Cardiovasc Eng, 2004

Conclusions

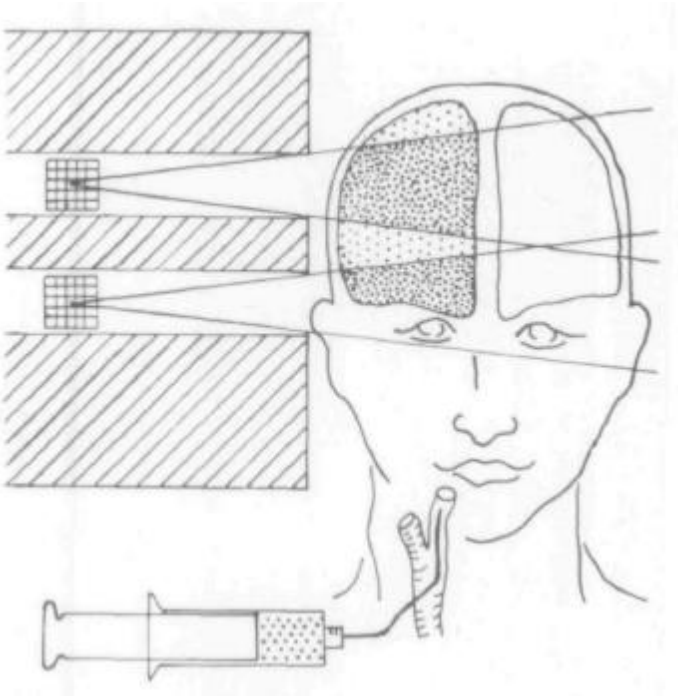
- Complicated:
  - Large inter-connected network of vessels
  - Redundancy at local and global level
- Simple:
  - Just altered by changes in vessel diameter

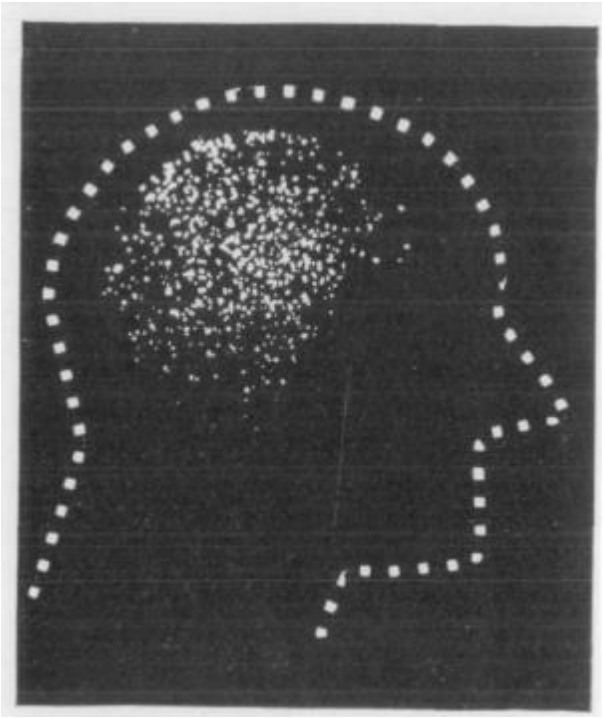
- Global versus local
- How can it be assessed at both levels?

3. MEASUREMENT TECHNIQUES

Early CBF techniques

- Inert indicators, usually Xe-133
  - Length of measurement of order 15 minutes

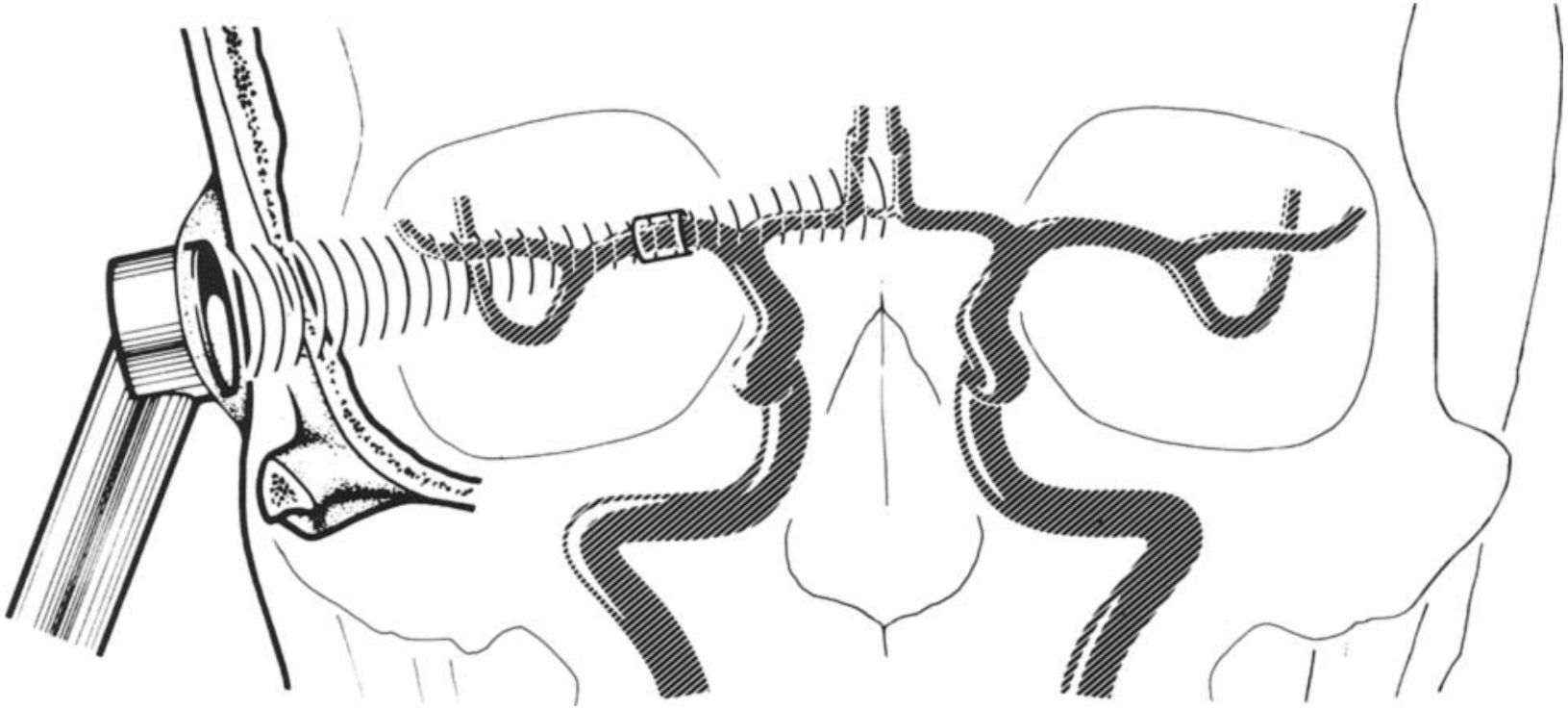




Ingvar and Lassen, Br J Anaesth, 1965

Transcranial Doppler

- TCD now most common measurement
- Usually used for Middle Cerebral Artery



Aaslid, J Neurosurg, 1982

Transcranial Doppler

- Advantages:
  - High temporal resolution
  - Quantification of dynamic cerebral autoregulation

- Disadvantages:
  - Measures CBFV, not CBF, and in just one vessel
  - Assumes vessel diameter does not change
  - Need an acoustic window

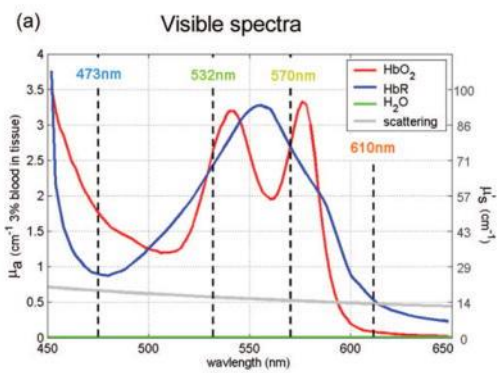
Transcranial Doppler

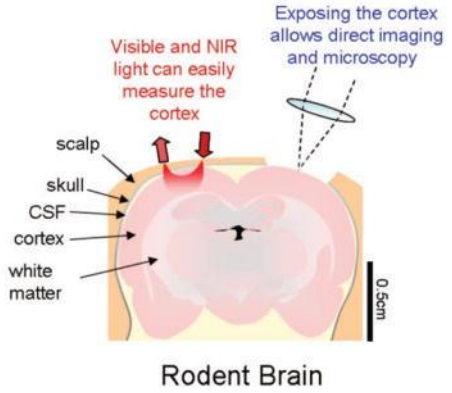
- Does vessel diameter change?

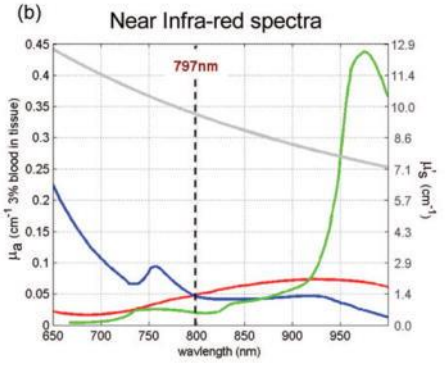
- To changes in pressure:
  - ICA yes, MCA no, ACA yes
- To changes in CO2:
  - ICA yes, MCA a little, ACA yes, VA no
- To changes in O2:
  - ICA no, VA no

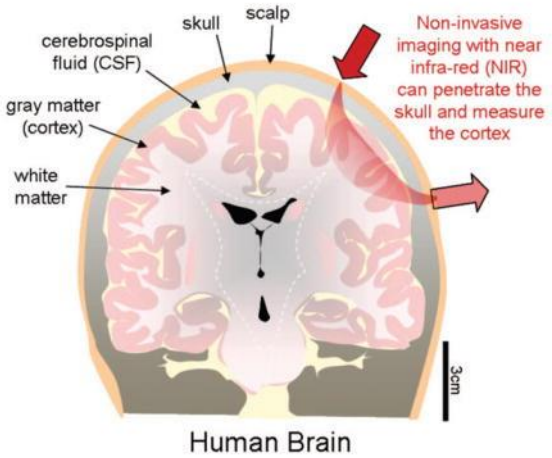
Near Infra-Red Spectroscopy

- First developed in 1977 by Jöbsis





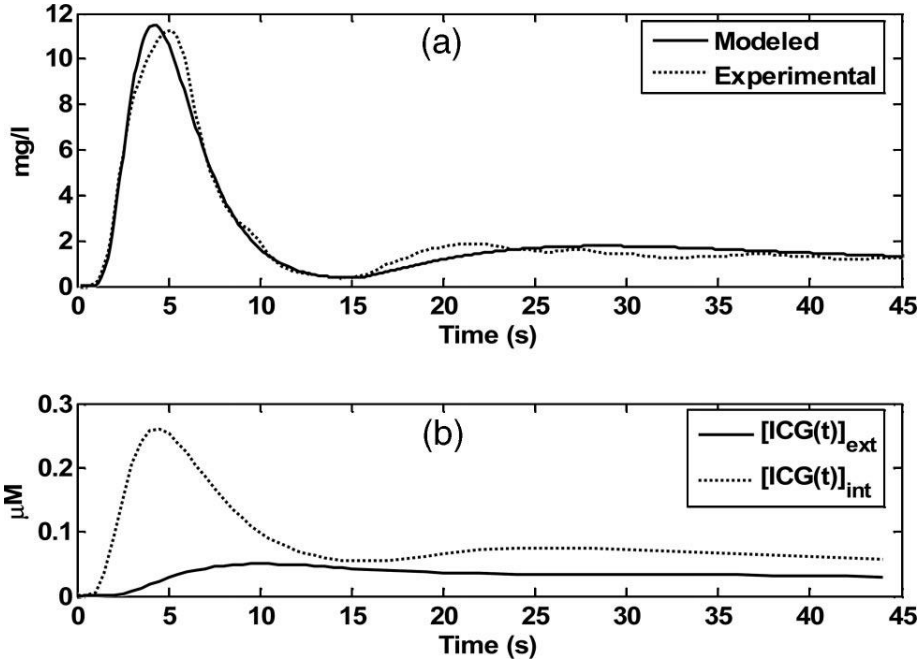




Hillman, J Biomed Opt, 2007

Near Infra-Red Spectroscopy

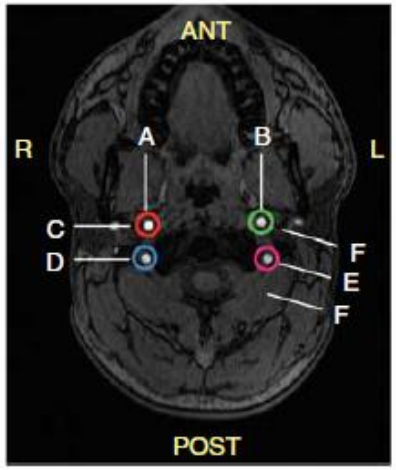
- CBF measured through bolus injection of Indocyanine Green:
  - Model needed
  - Extracranial component of measurement

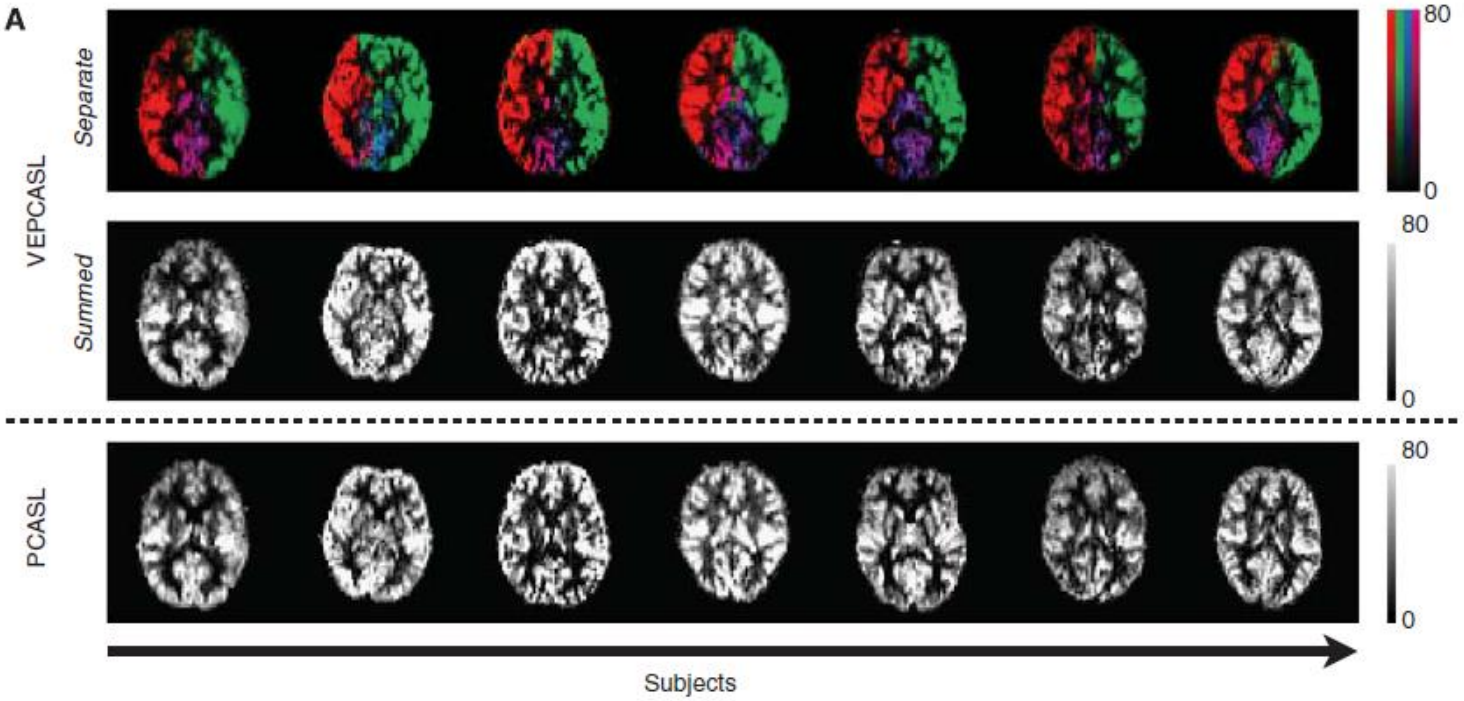


Leung et al., Appl Opt, 2007

Magnetic Resonance Imaging

- Vessel-Encoded Arterial Spin Labelling

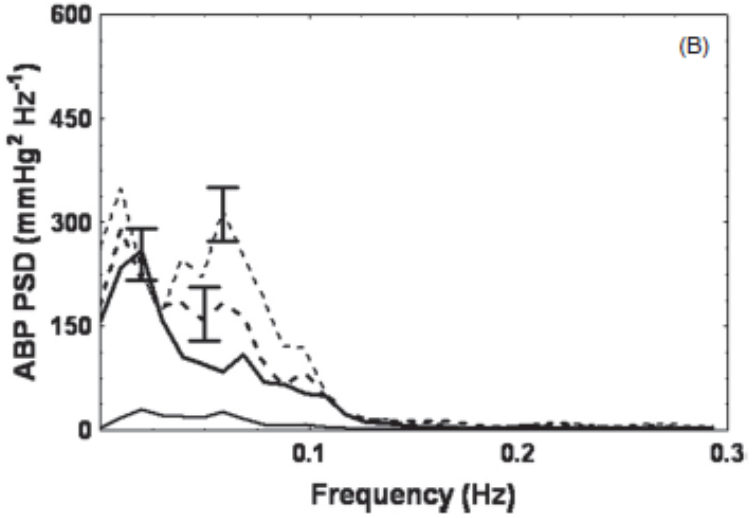




Okell et al., JCBFM, 2013

Autoregulation tests

- Need to manipulate ABP to get variability
- Six common methods:
  1. Random fluctuations in ABP
  2. Lower body negative pressure
  3. Thigh cuff
  4. Cold pressor
  5. Isometric hand grip
  6. Valsalva manoeuvre



Katsogridakis et al., Phys Meas, 2012

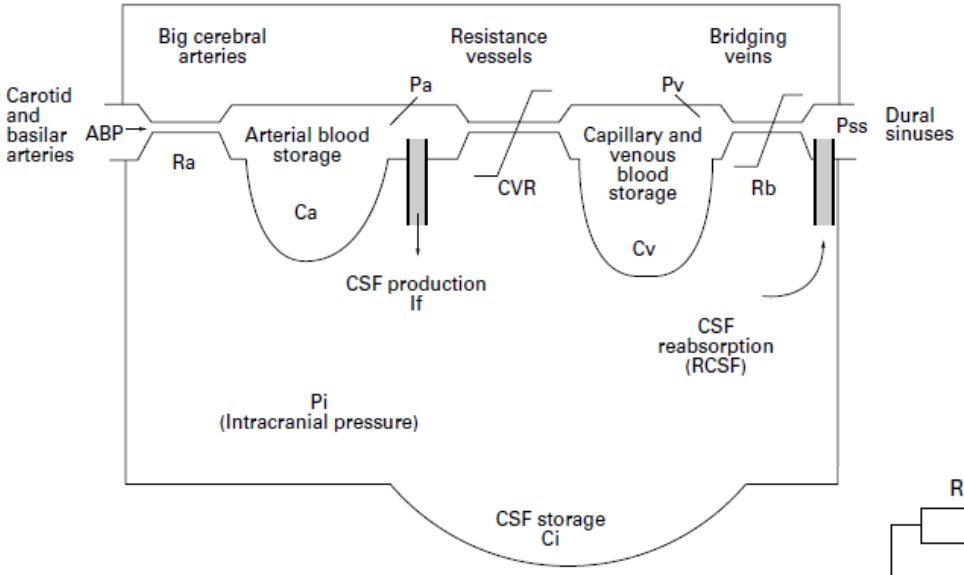
Conclusions

- Multiple ways to measure both ABP and CBF/V
- ABP:
  - Many devices
  - No non-invasive gold standard
- CBF/V:
  - Either good temporal or good spatial resolution
  - Difficulty converting between CBF and CBFV

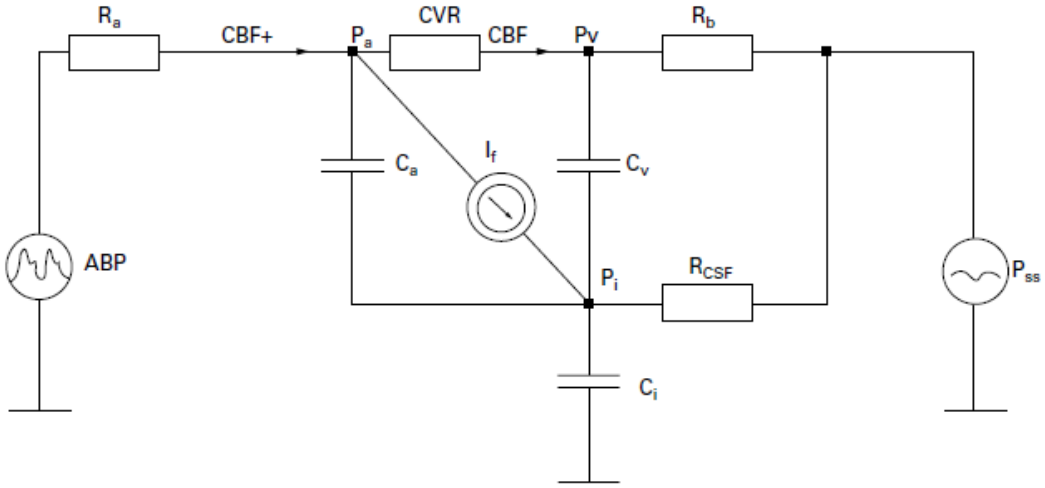
4. MODELS

Lumped parameter models

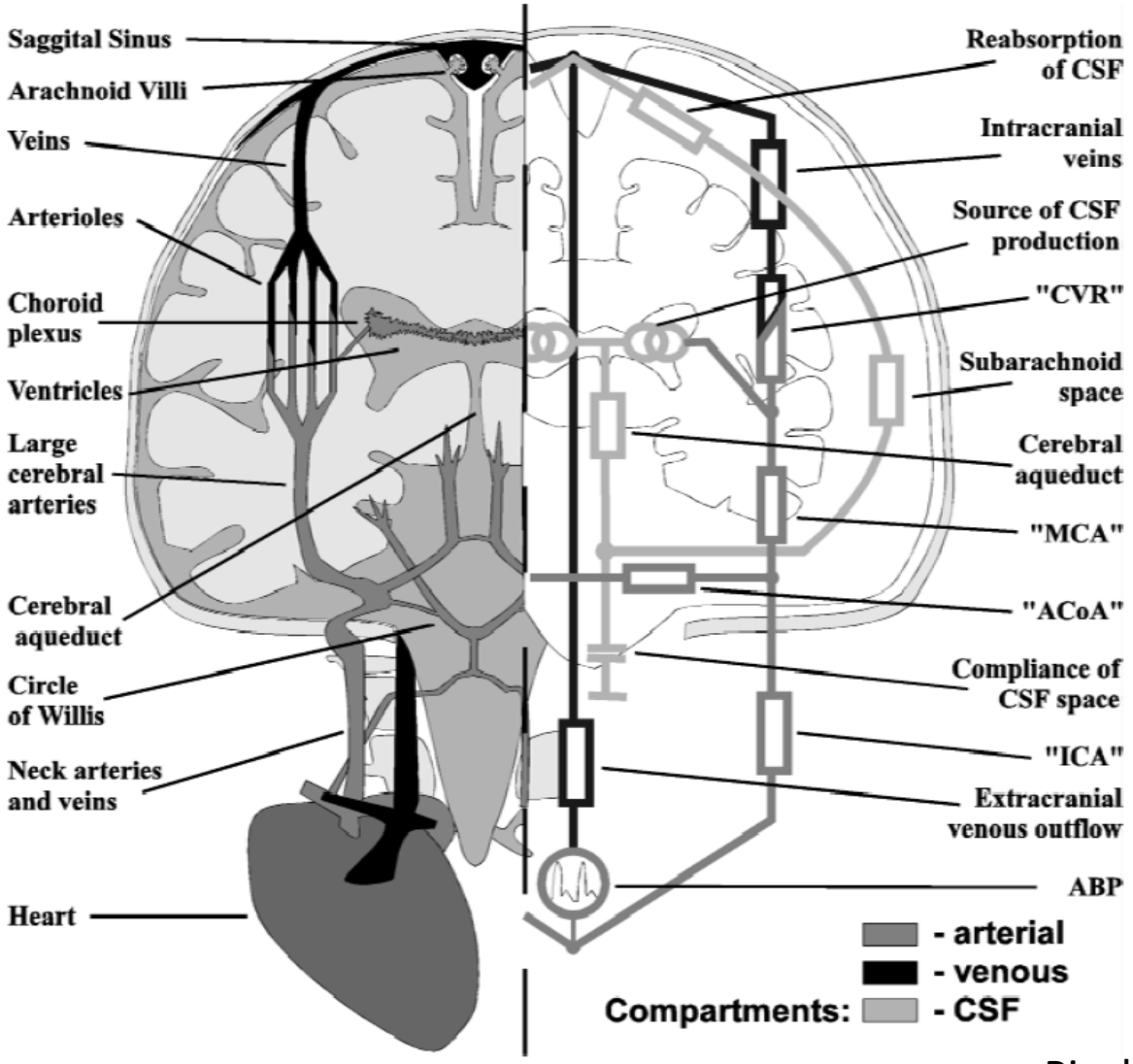
- Equivalent electrical circuit concept



Czosnyka et al., JNNP, 1997

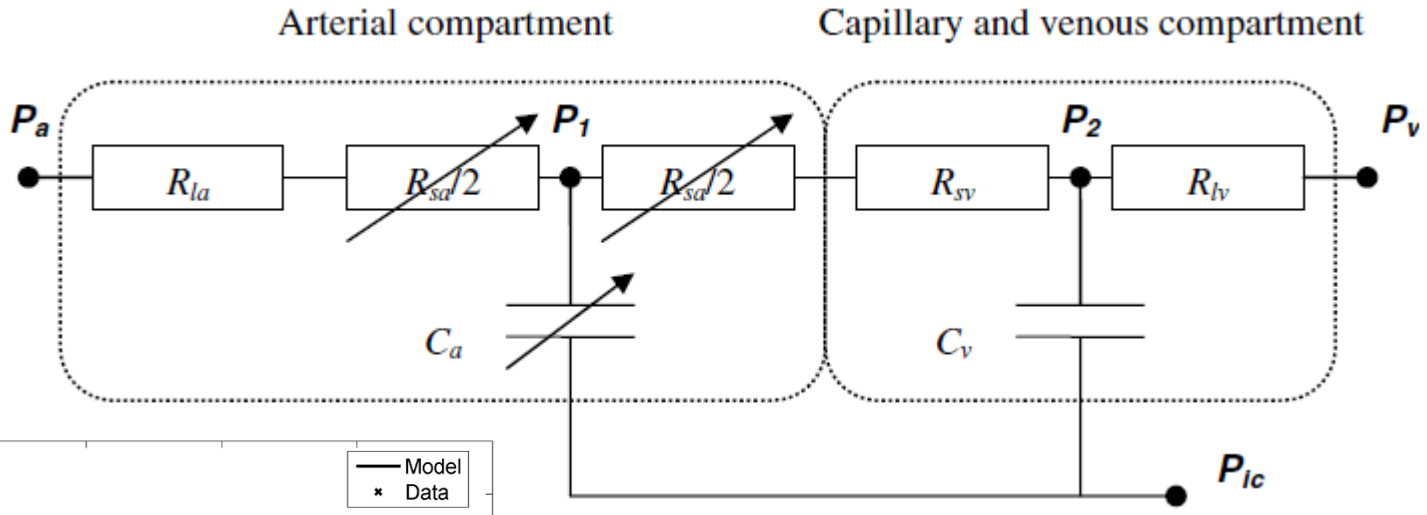


Whole brain models

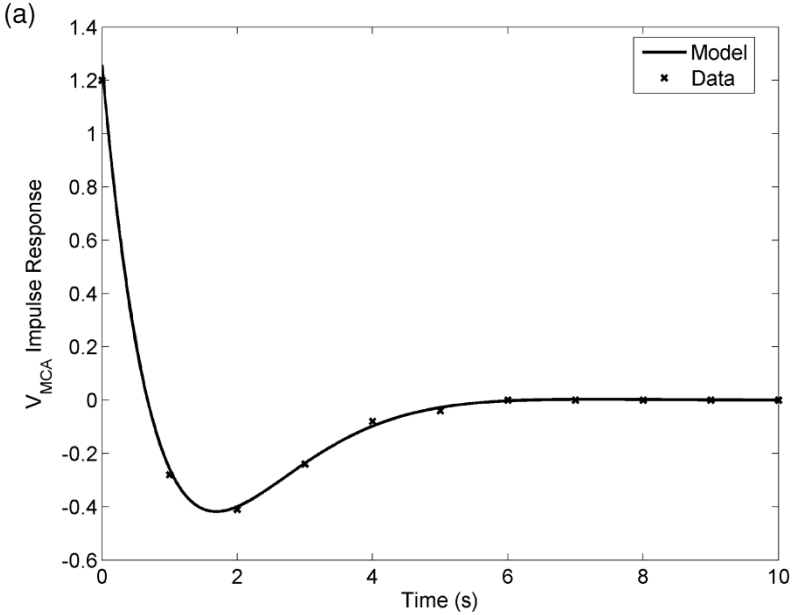


Piechnik, JCBFM, 2001

Whole brain models



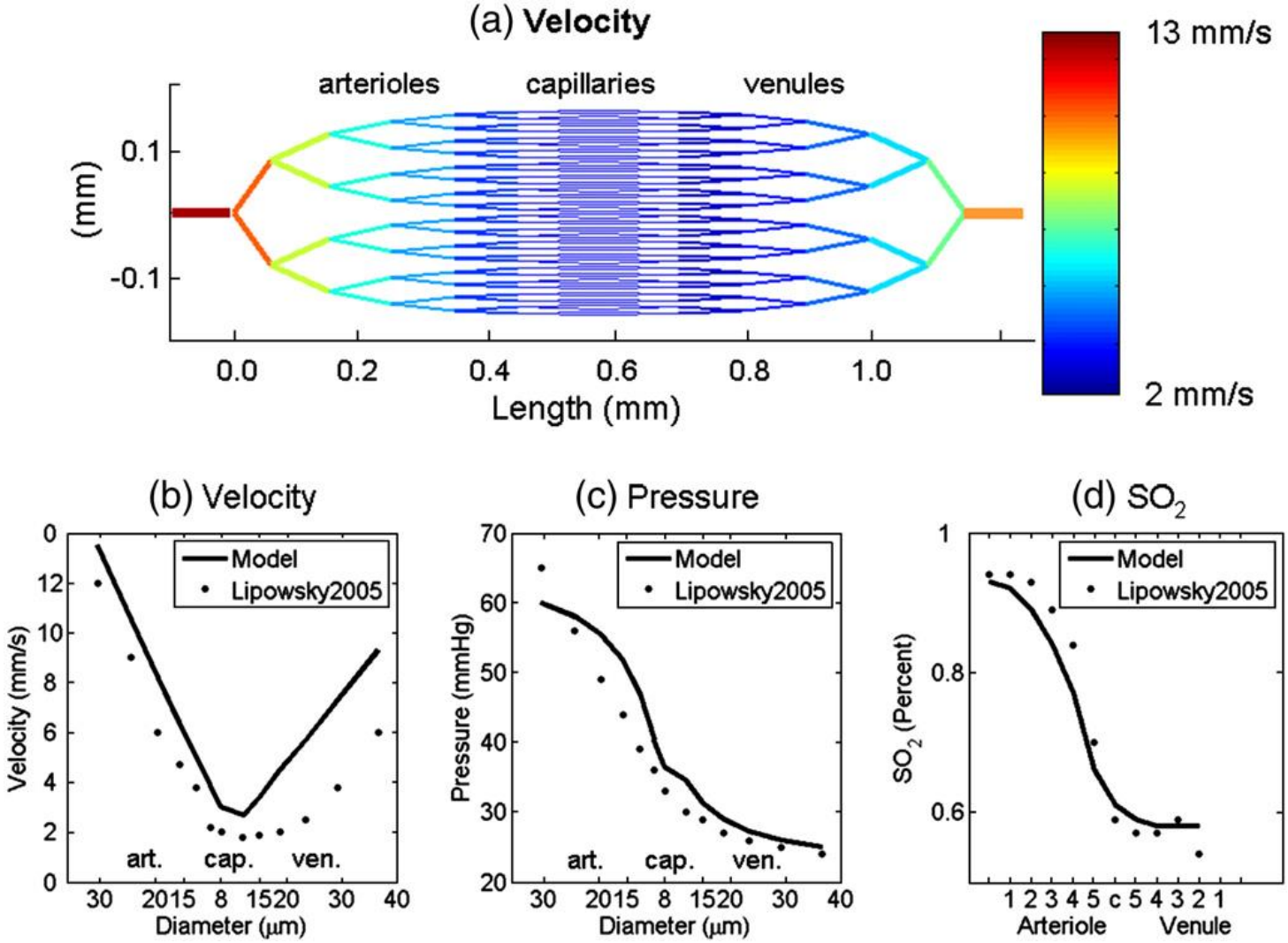
(a)



$$J(s) = \frac{1}{\beta_1}\left[1 + \frac{(1-\beta_1)(1-\alpha_1) - 2\left(\frac{\alpha_2}{1+s\tau}\right)}{\beta_1(1+\alpha_1) - (1-\beta_1)(1-\alpha_1 - s\alpha_1\tau_a) + \left(\frac{\alpha_2}{1+s\tau}\right)(2 - s\alpha_1\tau_a)}\right]. \quad (24)$$

Payne, MBS, 2006; Payne and Tarassenko, ABME, 2006

Network models



Boas et al., Neuroimage, 2008

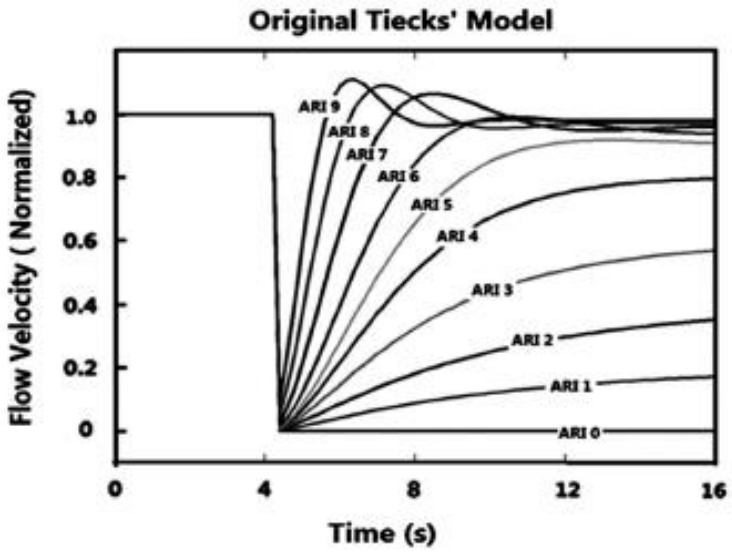
Conclusions

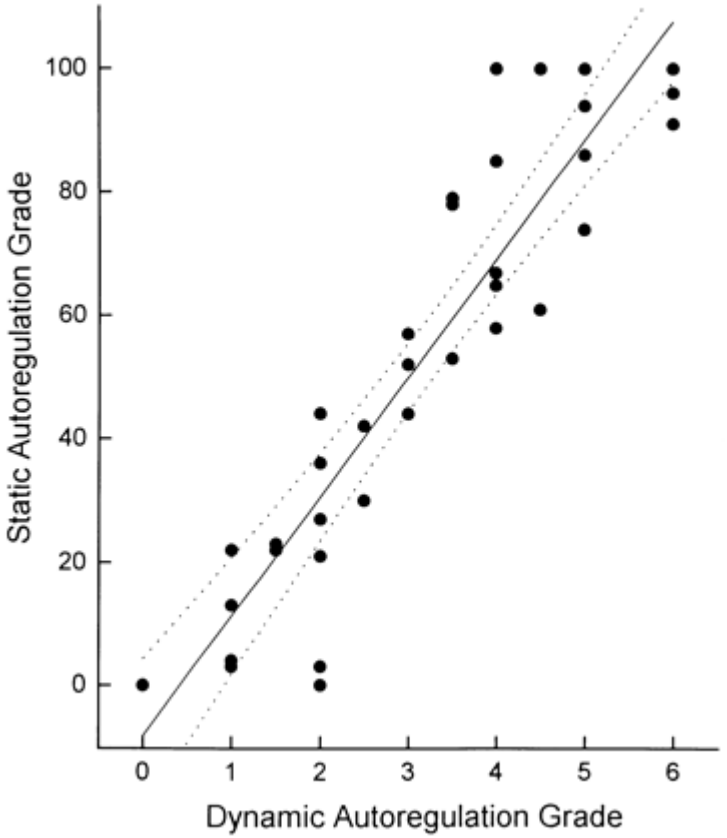
- Many models presented to model cerebral autoregulation
  - Very simple to very complicated
  - Balance between understanding and utility
  - Difficulty lies in interpretation and relationship to data
- Modelling still some way behind analysis

5. ANALYSIS

Time domain

- Tiecks model

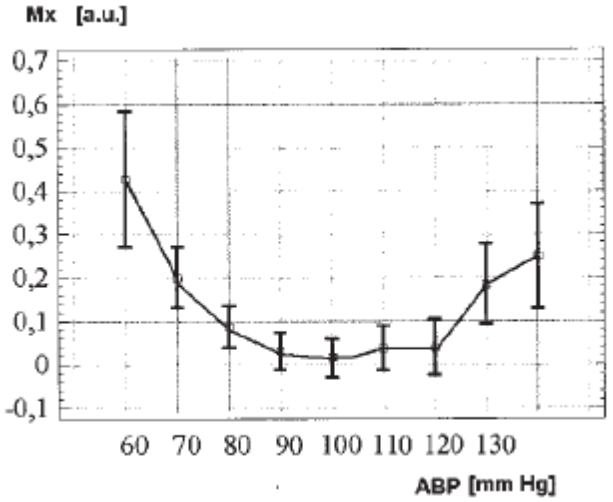


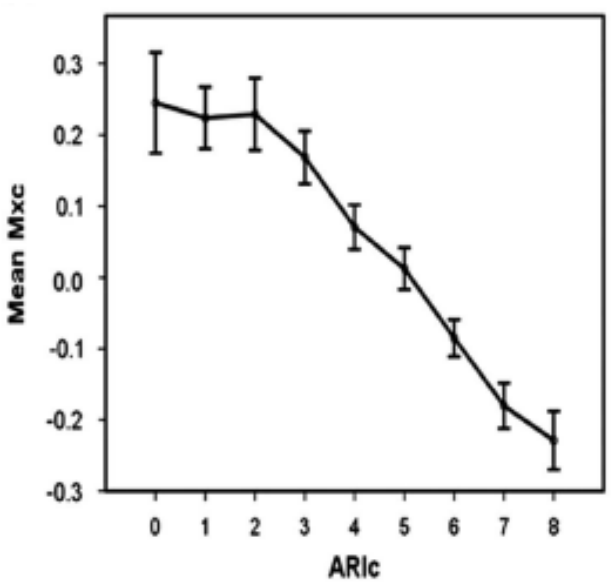


Liu et al., JCBFM, 2014; Tiecks et al., Stroke, 1995

Correlation coefficient

- Mx = short-term correlation for ABP and CBFV

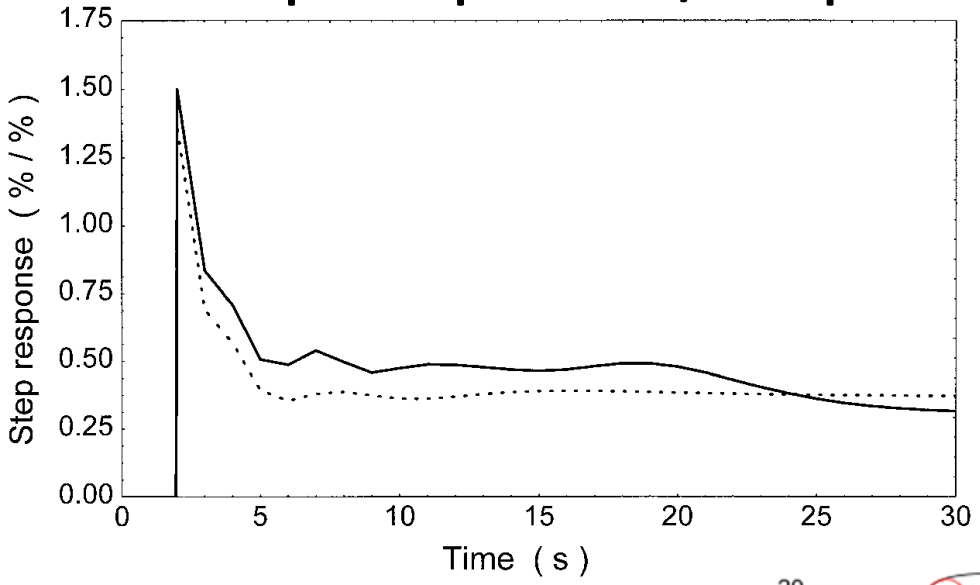


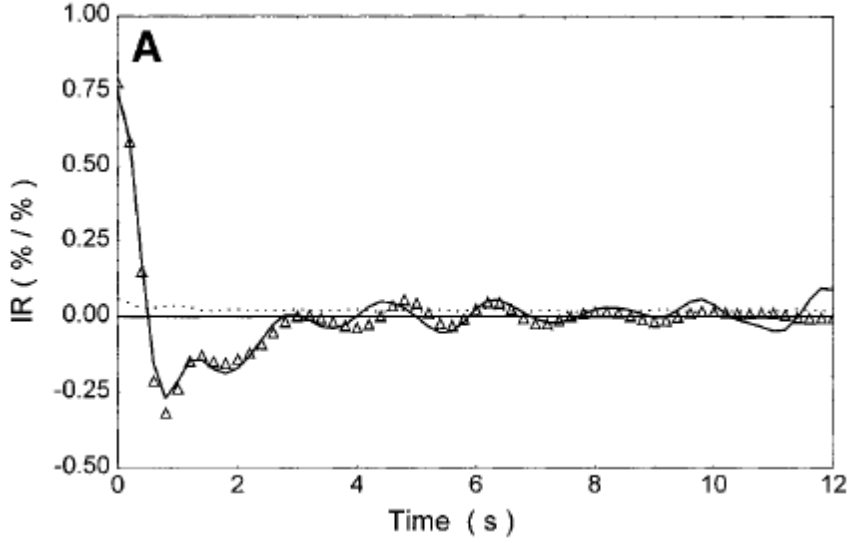


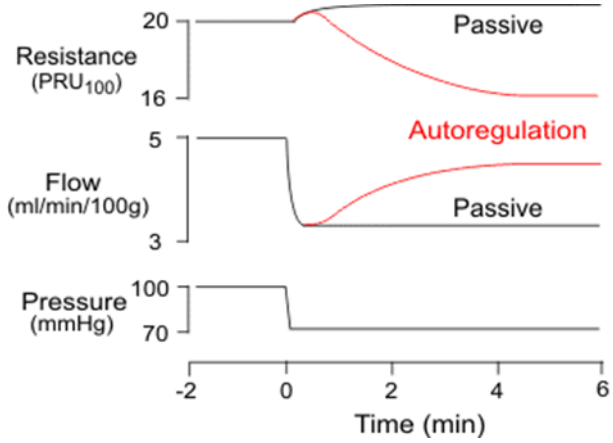
Czosnyka et al., J Neurosurg, 2001; Liu et al., JCBFM, 2014

Frequency domain

- Step response / impulse response



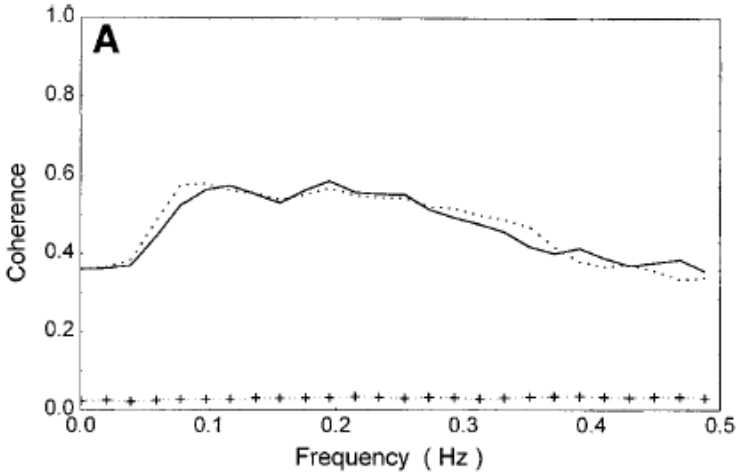


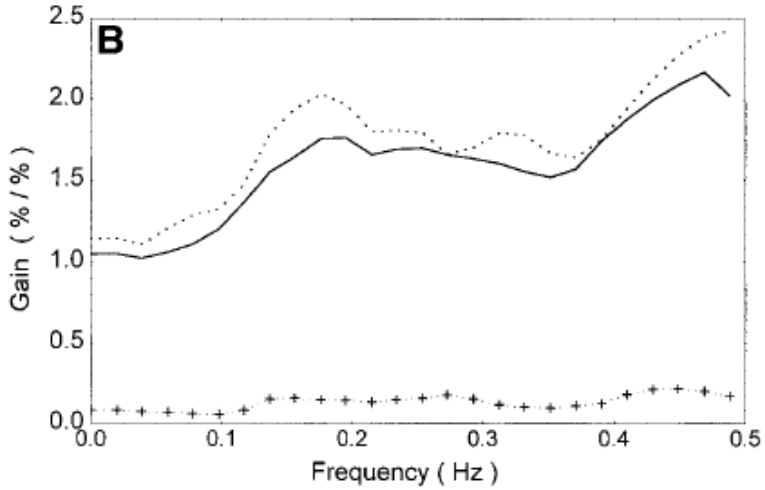


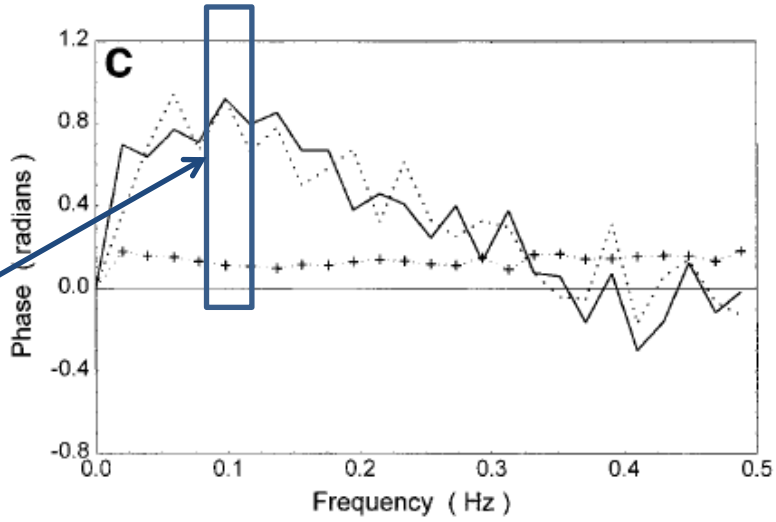
Panerai et al., AJP, 1999

Frequency domain

- Transfer function analysis:
  - gain / phase / coherence







Phase at 0.1 Hz

Panerai et al., AJP, 1999

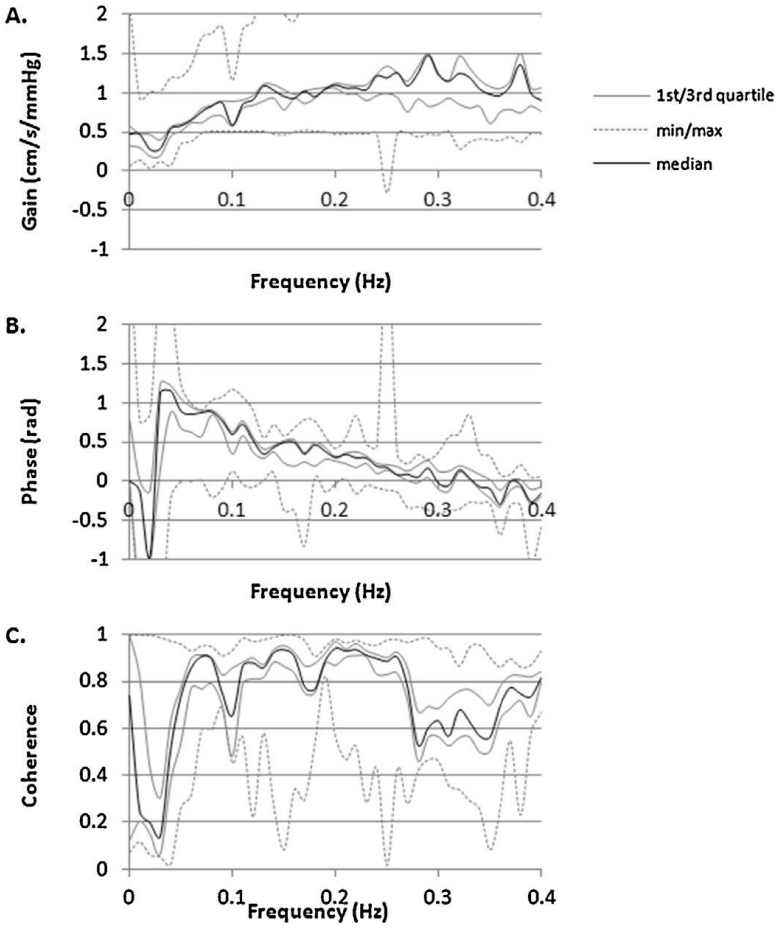
More advanced methods

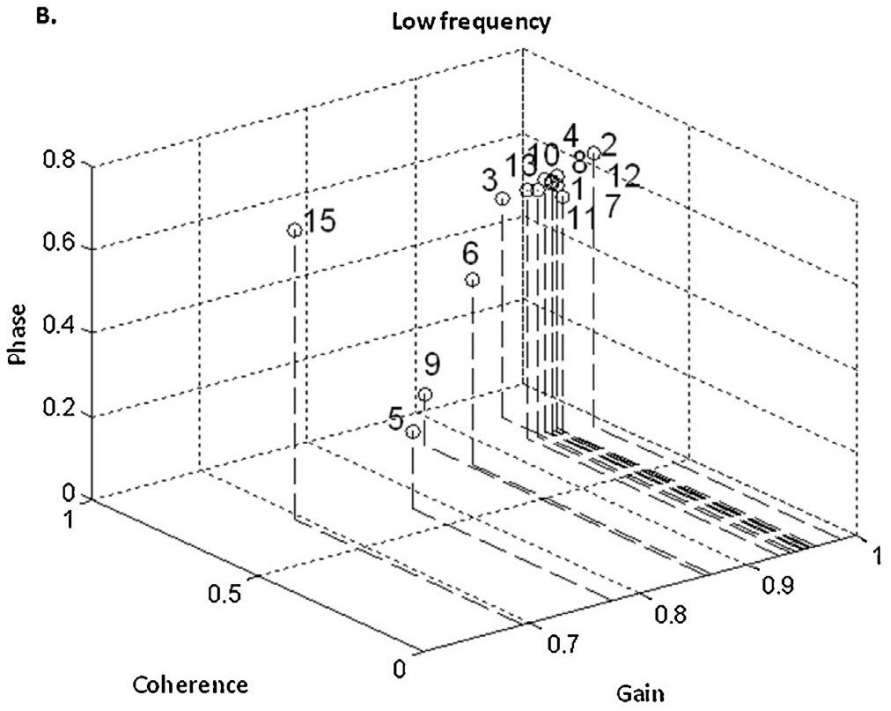
- Number of other more complex methods:
  - Non-stationary models:
    - Short-time Fourier transform
    - Wavelet analysis
  - Non-linear models:
    - Laguerre-Volterra network
    - Transfer entropy
    - Bispectral analysis

- Difficulty in validation (very large data volume)

Variability

- First large centre (#=15) study
  - 50 healthy subjects analysed

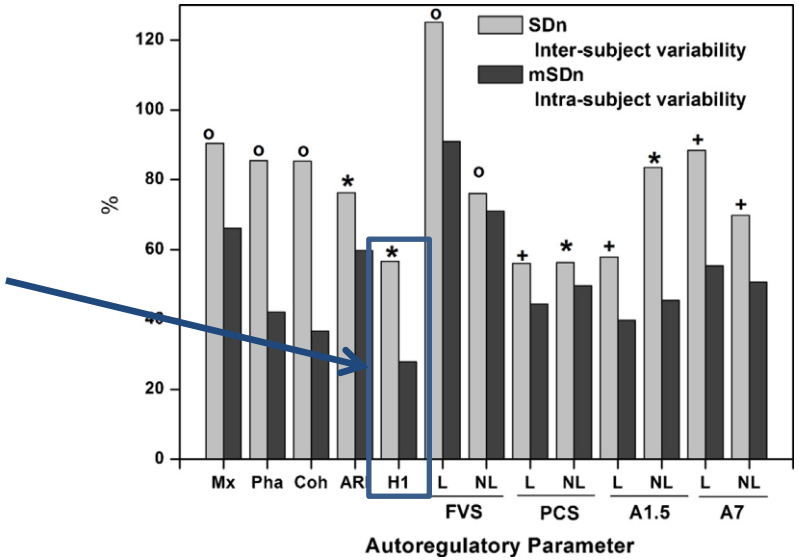




Van den Abeelen et al., MEP, 2014

Conclusions

- Many ways to analyse relationship between ABP and CBFV
- Simple ones are (often) most useful
  - ARI
  - Phase angle
  - H1



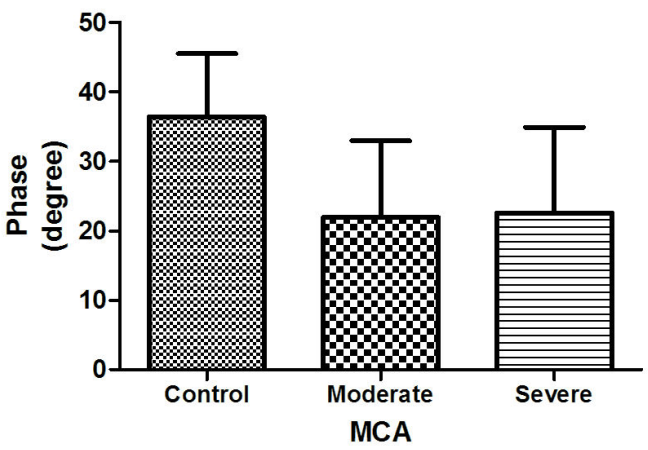
- Balance between value and insight

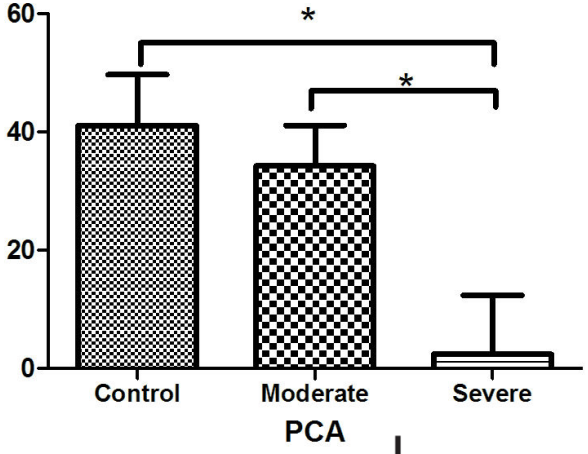
Angarita-James et al., MEP, 2014

6. CLINICAL PRACTICE

Stenosis

- Effect dependent upon occluded vessel





Gong et al., PLOS1, 2013

Table 2. Results of RoRc, phase shift, magnitude, coherence and CVR in controls and different degree of MCA stenosis.

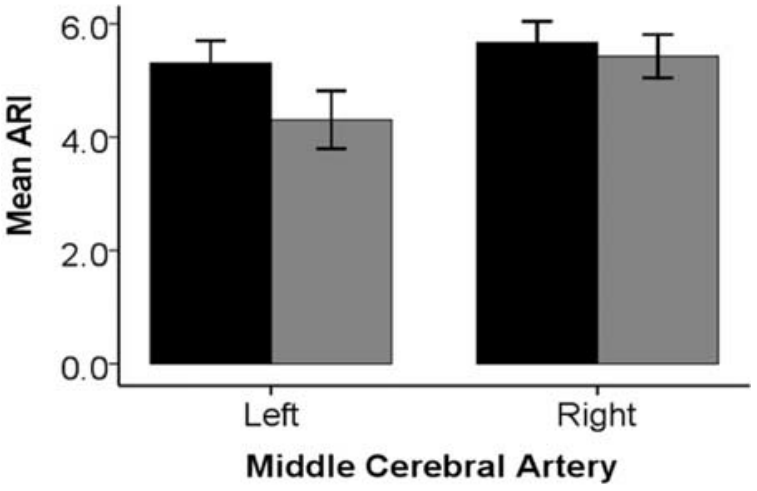
		Degree of MCA Stenosis		
	Controls	Mild	Moderate	Severe
	(n = 38)	(n = 8)	(n = 11)	(n = 13)
RoRc(%/s)	39.62±27.99	29.81±16.10	17.76±8.21*	1.16±13.22*
Gain (ampl.)	0.58±0.35	1.30±1.34*	0.70±0.42	0.42±0.20
Phase (degree)	55.66±22.10	42.37±13.10	26.93±15.67*	6.88±14.14*
Coherence	0.51±0.18	0.51±0.15	0.56±0.20	0.52±0.23
CVR(%/mmHg)	2.18±0.80	2.76±0.85	1.53±0.84*	0.98±0.67*

MCA, middle cerebral artery; RoRc, rate of recovery, CVR: cerebrovascular reactivity;
*$p<0.05$, compared with normal controls.
doi:10.1371/journal.pone.0088232.t002

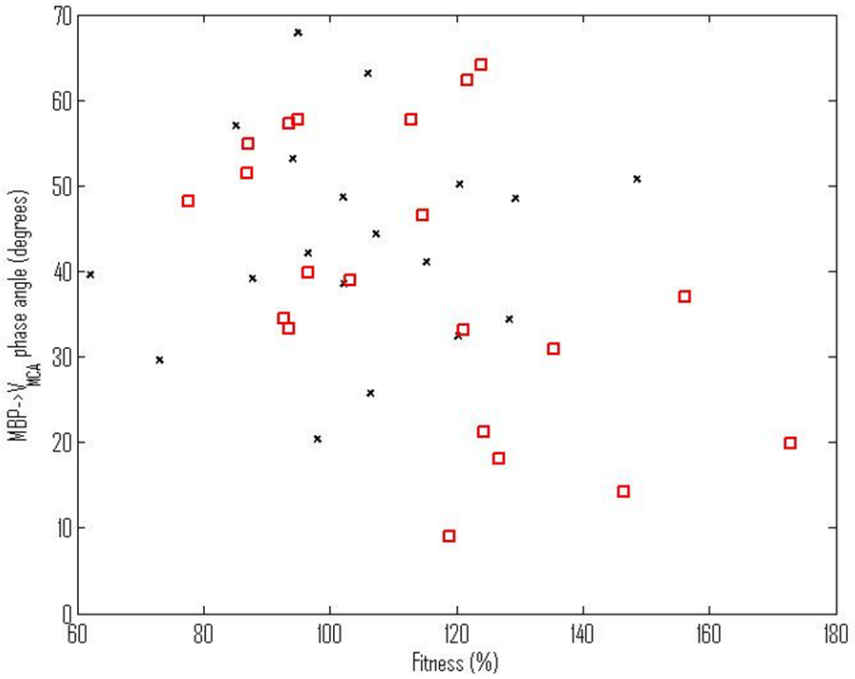
Chen et al., PLOS1, 2014

Ageing / fitness / exercise

- Not affected in ageing; not affected by fitness



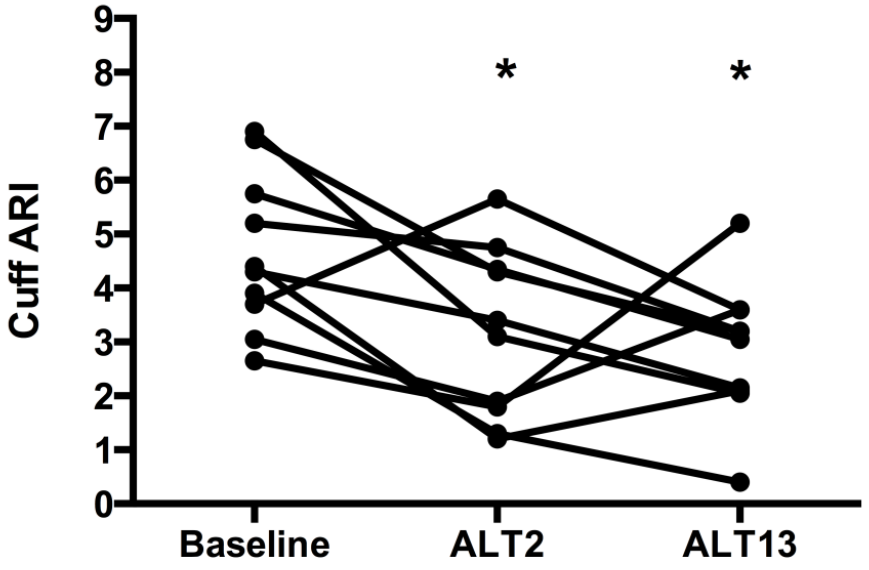
Dineen et al., AgeAgeing, 2011

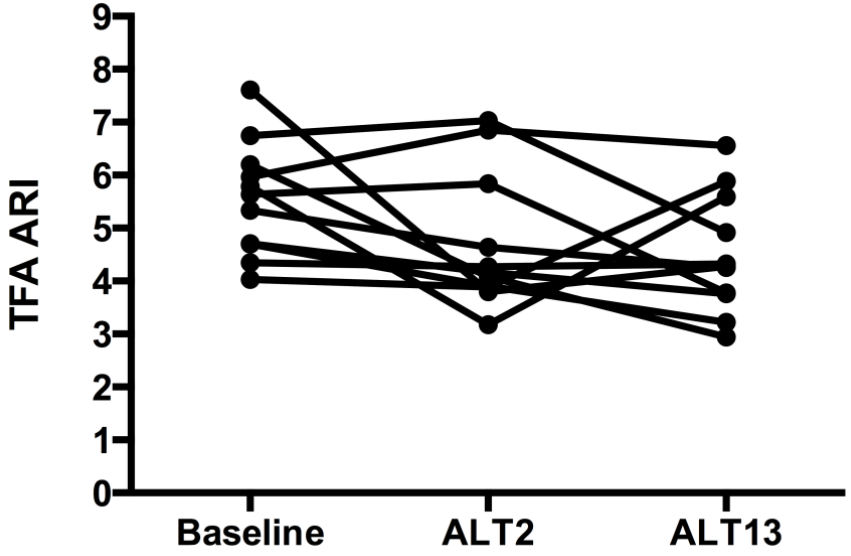


Payne et al., unpublished

Altitude

- Affected somewhat at altitude





Subudhi et al., ExpPhysiol, 2014

Brain trauma and injury

- Highly variable, but predictive of outcome

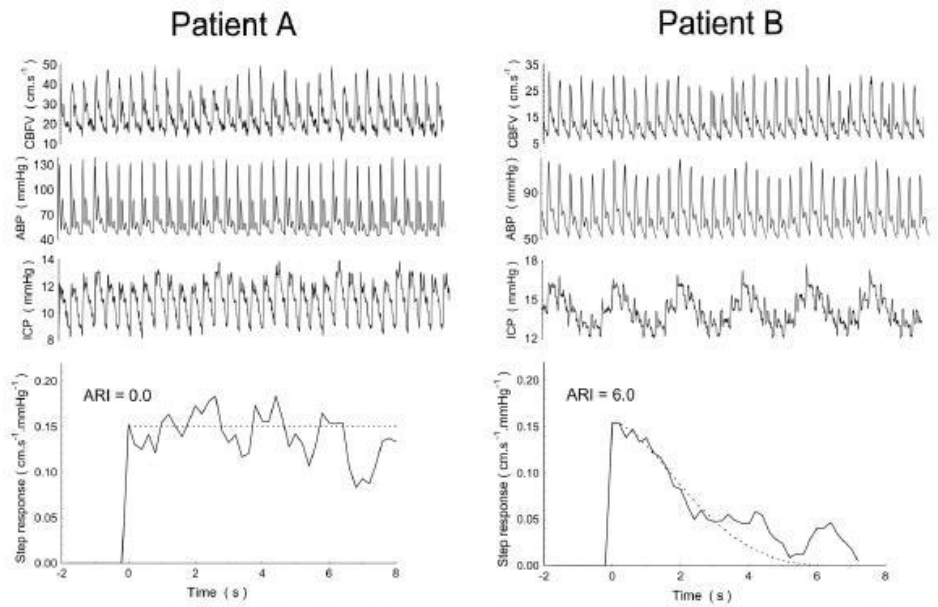


FIG. 1. (Top) Representative recordings of CBFV, ABP and ICP from two different patients. (Bottom) Corresponding CBFV responses to a step change in ABP (continuous line) and Aaslid's model response fitted to the first 2 s of the step response (dashed line).

TABLE II. Distribution of ARI according to three grouped categories of GCS

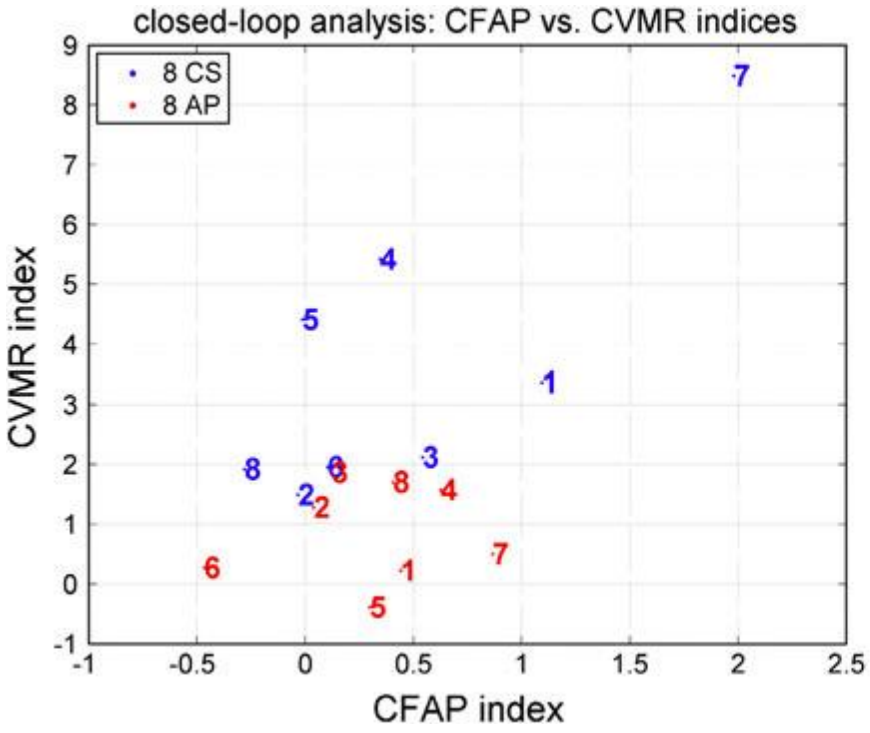
GCS	Survivors mean ± SD (*n*)	Non-survivors* mean ± SD (*n*)
3–4	5.89 ± 2.76 (7)	3.51 ± 2.73 (7)
5–6	6.62 ± 1.97 (7)	2.31 ± 3.28 (2)
7–8	6.34 ± 0.65 (3)	3.92 ± 3.40 (3)

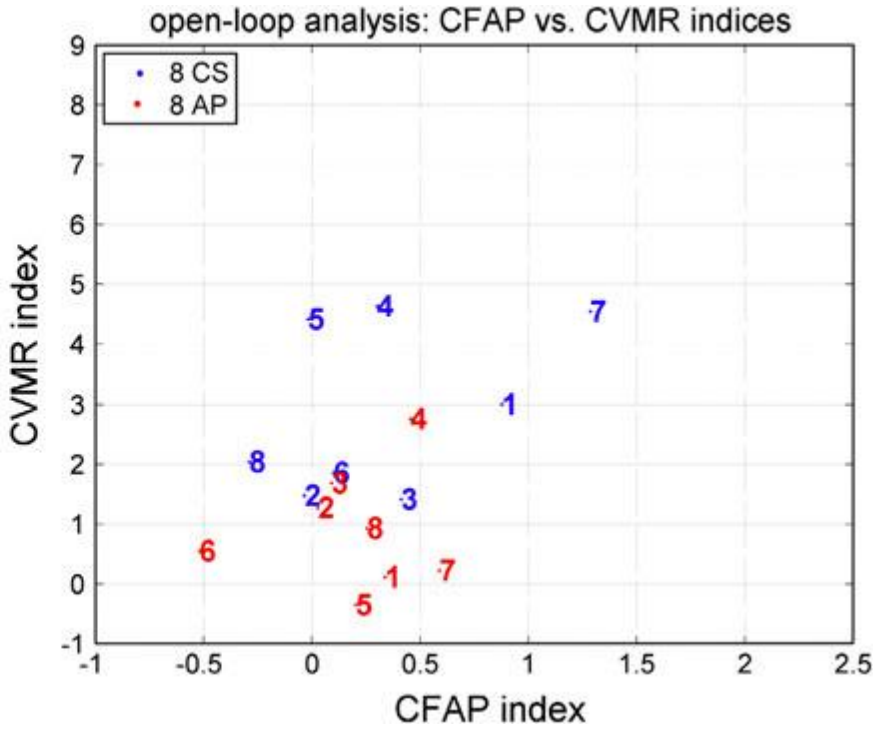
*$p = 0.028$ for combined p-values (see text).

Panerai et al., BrJNeurosurg, 2004

Dementia

- Some indications of impairment





Marmarelis et al., ABME, 2013

Stroke

- Dynamic but not static autoregulation affected

Table 4. Comparison of patient and control dynamic and static test ARIs

Test	Stroke		Controls	Two-sample t test		General linear model	
	non-affected hemisphere (NonS)	affected hemisphere (S)		NonS	S	NonS	S
Dynamic test ARI							
Thigh cuff release (n = 41, 37, 48)	4.81 ± 3.08	4.09 ± 3.32	6.18 ± 2.34	0.022	0.0018	0.011	0.000
Static tests ARI							
Isometric hand grip, % (n = 37, 36, 45)	57.8 ± 31.1	59.0 ± 34.0	51.5 ± 36.9	NS	NS	NS	NS
Thigh cuff inflation, % (n = 36, 35, 45)	65.9 ± 37.5	54.1 ± 36.5	52.2 ± 36.9	NS	NS	NS	NS

Results presented as means ± SD. n = Number of stroke subjects (non-affected = NonS, affected hemisphere = S) and control subjects with ARI results. Some subjects were excluded because of data selection criteria (see Data Analysis). Significance level $p < 0.05$ for differences between strokes and controls.

Dawson et al., CerebrovasDis, 2000

Conclusions

- Cerebral autoregulation is affected in many pathological states, but:
  - Difficulty in comparing studies with different assessment tools
  - Is this the driver of change or the marker?
  - How valuable is this in diagnosis and treatment?

- We have far to go in interpreting cerebral autoregulation in these conditions

7. CONCLUSIONS

Conclusions

- Cerebral autoregulation is complex
  - Simple control method in a complex system
  - Highly multi-factorial
  - Easy to measure something but difficult to quantify autoregulation
  - Stationary and linear (most of the time)

- Still a need for defining gold standards and trying to move the field forward in a more integrated and coherent manner

Open questions

- Need to settle on what metrics are ‘best’ and most valuable in clinical context
- Need to track variations over time and discern relationship with outcome
- Need to disentangle global and local control mechanisms
- Need to relate this all to clinical practice and therapy through large scale studies