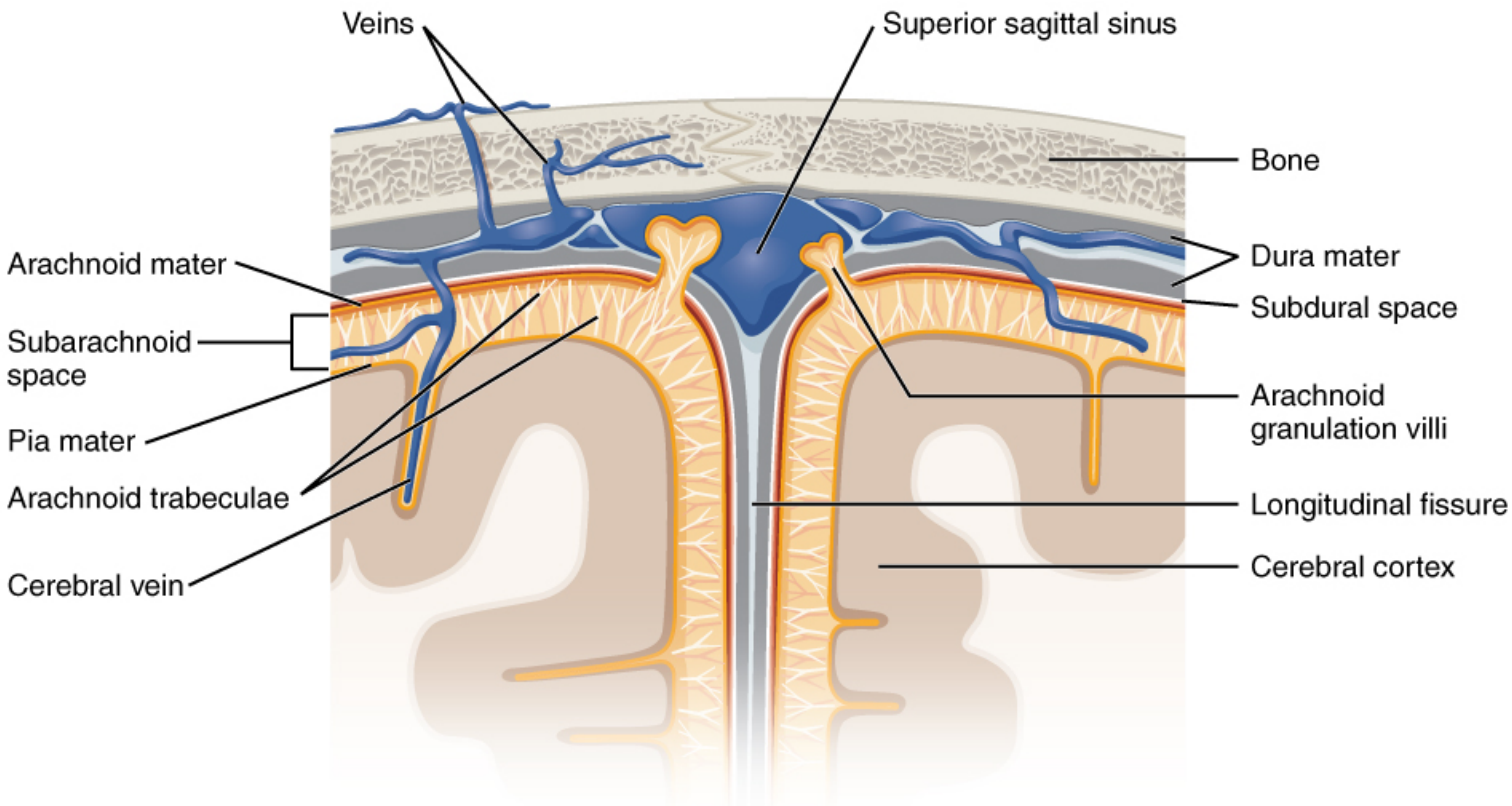
Kashif, F. M., Verghese, G. C., Novak, V., Czosnyka, Heldt, T (2012) Model-based noninvasive estimation of intracranial pressure from cerebral blood flow velocity and arterial pressure. *Sci. Transl. Med.* 4(129): 129ra44

ICP is the hydrostatic pressure of the CSF surrounding the brain

- Elevated ICP is a common condition in NICUs
- brain edema, intracranial hemorrhage, brain tumors,…
- brain herniation
- brain death

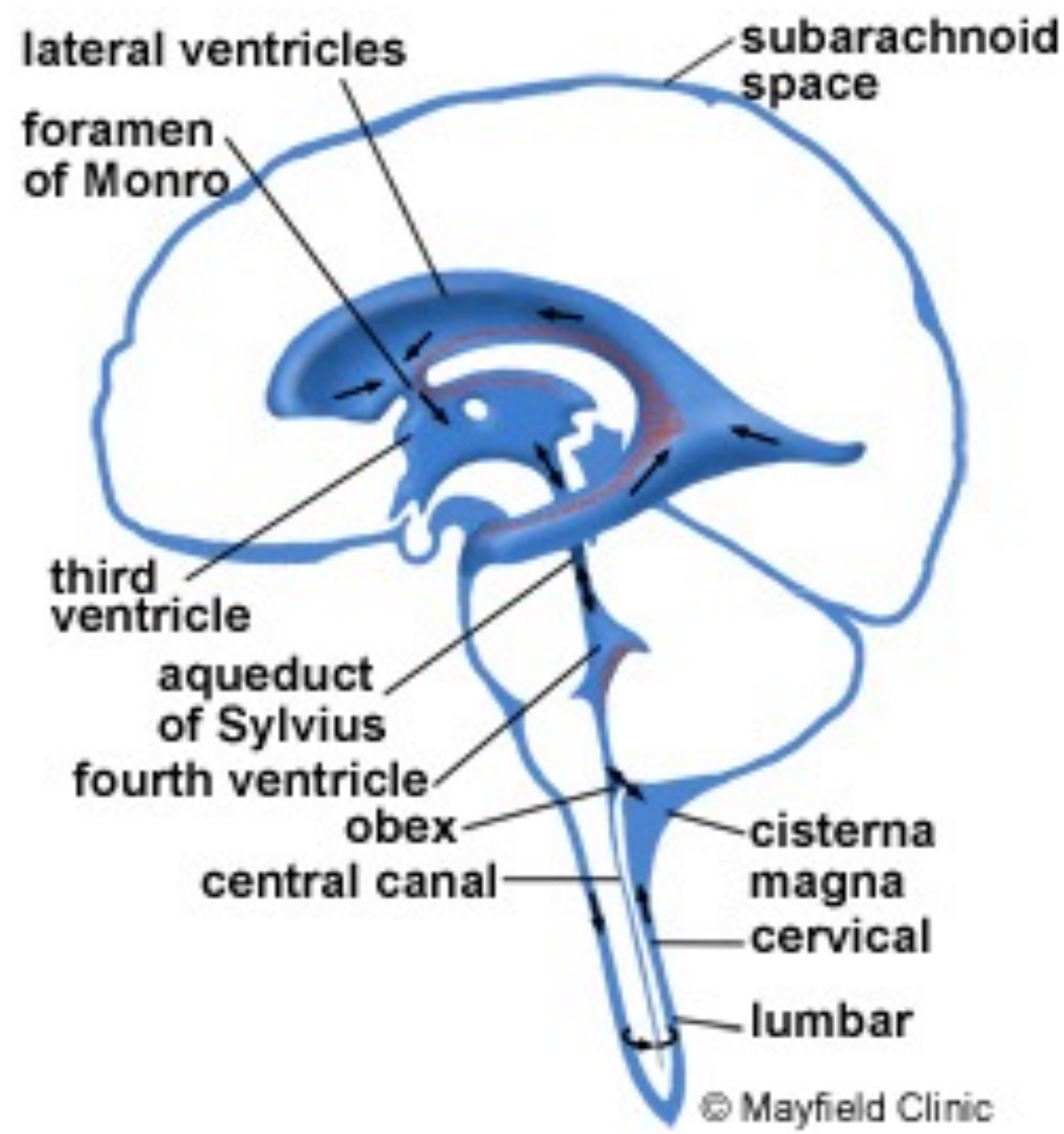
- Expansion of optic disk
- pupillary reflex
- placement of sensor on brain
- placement of catheter through brain into ventricles

By the time these invasive procedures for monitoring ICP are warranted, it can be too late

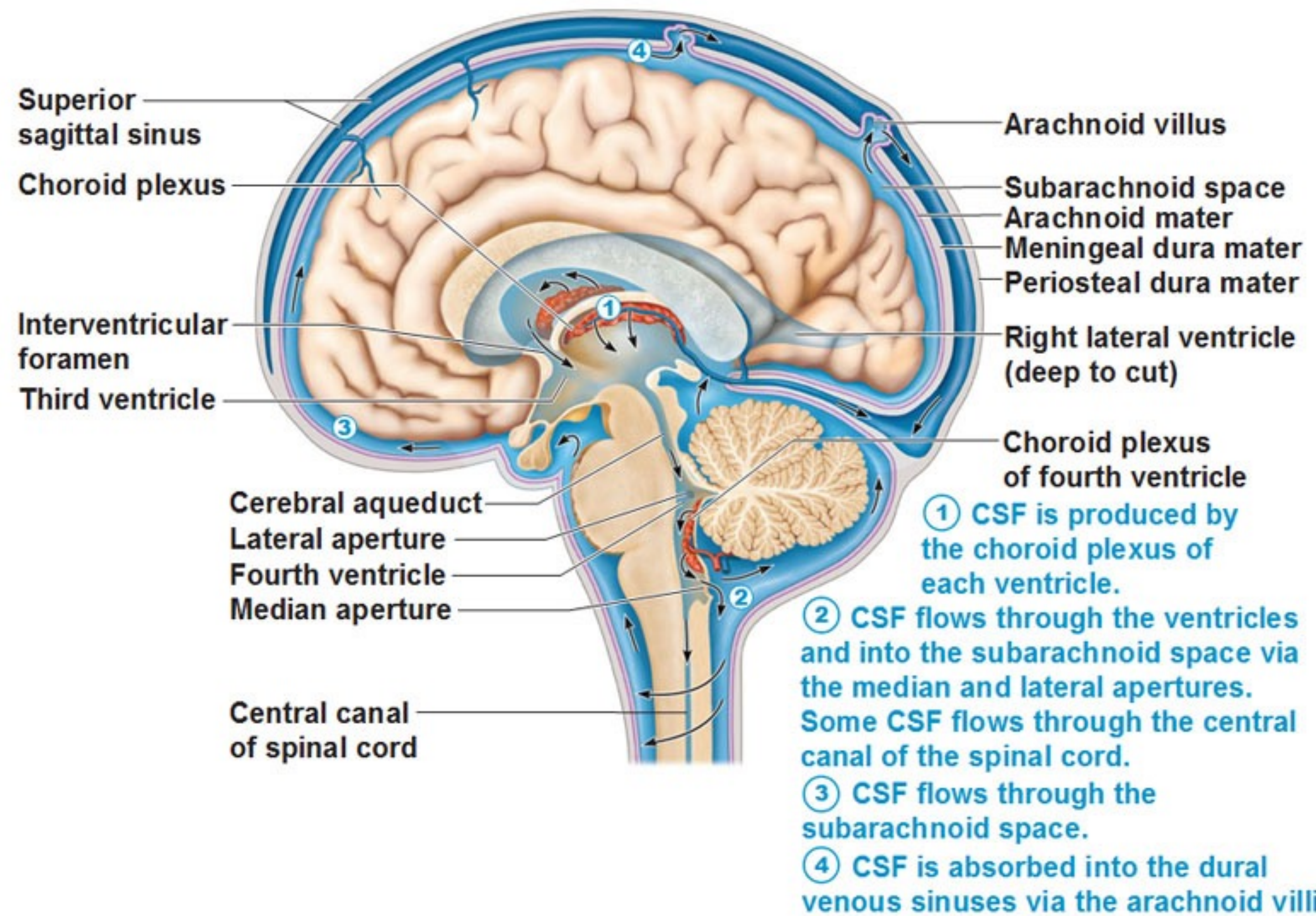


Arachnoid is one of 3 (dura; arachnoid; pia) brain meninges (membranes)
Sub-arachnoid space is between arachnoid and pia
CSF is in the sub-arachnoid space
CSF is created from blood plasma in the choroid plexi of the brain ventricles

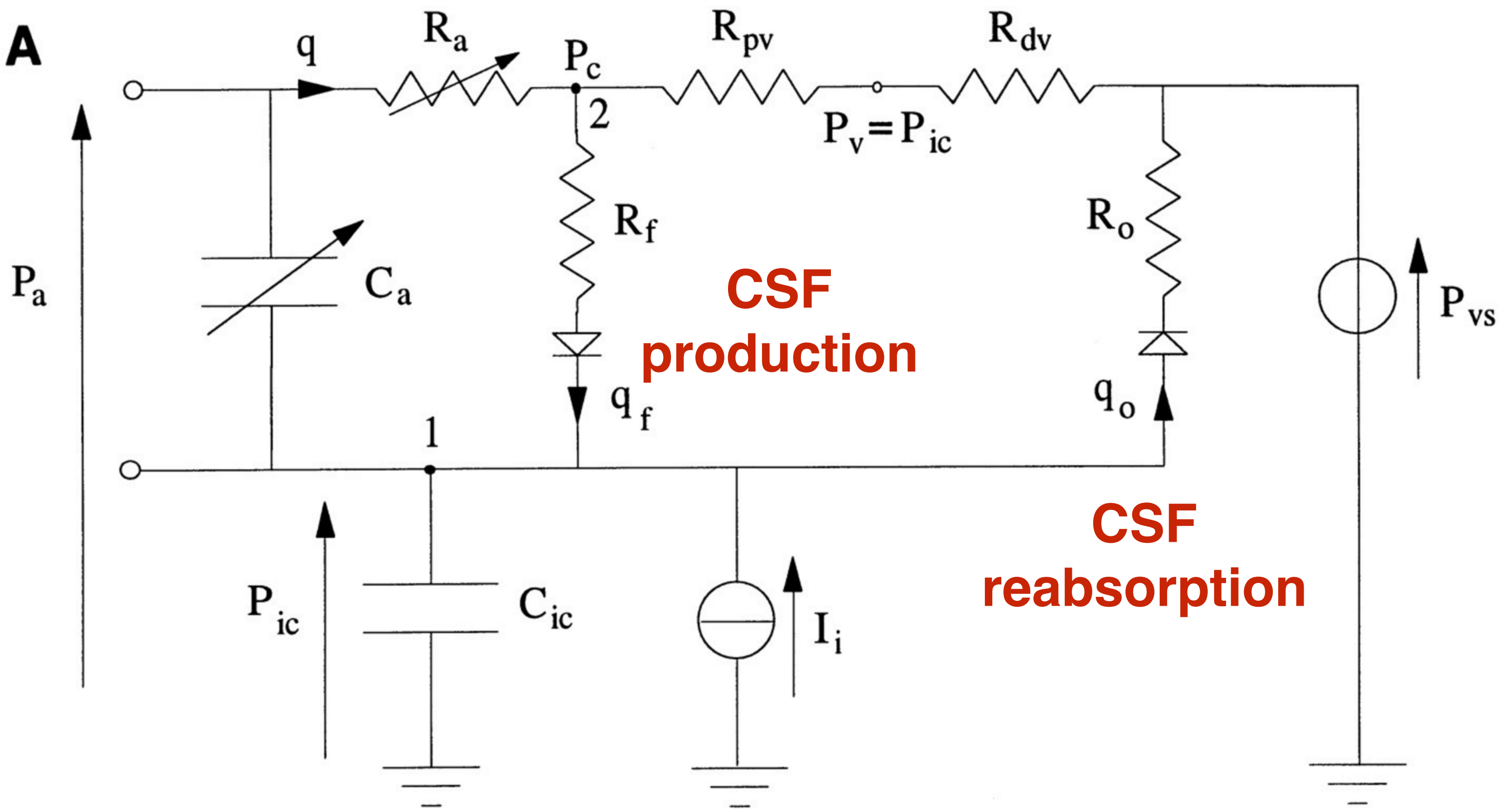
Note that the veins enlarge to form sinuses (superior saggital sinus is shown)
Lots of CSF re-enters the blood in this sinus



Circulation of Cerebrospinal Fluid (CSF)



Ursino, M., Lodi, C. A. (1997) A simple mathematical model of the interaction between intracranial pressure and cerebral hemodynamics. *J Appl Physiol.* 82(4): 1256



P_{ic}= ICP
C_{ic}= CSF volume stored on the intracranial compliance
P_{vs} = venous sinus pressure

P_a= arterial pressure entering brain, ~ = systemic arterial pressure
q = blood flow into brain vascular network
C_a = Variable cerebro-arterial-arteriolar compliance
R_a = Variable cerebro-arterial-arteriolar resistance
P_c = Capillary pressure
R_f = Capillary pressure drives production of CSF (chorid plexus) through R_f
R_o = determines flow of CSF back into blood (q_o)
R_{pv} = proximal venous resistance
R_{dv} = sinus venous resistance
P_v = cerebral venous pressure equals ICP
P_{vs} = venous sinus pressure

Ursino, M., Lodi, C. A. (1997) A simple mathematical model of the interaction between intracranial pressure and cerebral hemodynamics. *J Appl Physiol.* 82(4): 1256

What about R_a and C_a? We said they are regulated.

- decrease in cerebral blood flow q causes vasodilation and R_a decreases
- decrease in q causes increased compliance C_a
- an increase in q causes vasoconstriction, R_a increases
- an increase in q causes decreased compliance Ca

Governing equations arise from application of Kirchoff's current Law at each nodes and some underlying conservation relationships

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$$C_{ic} \cdot \frac{dP_{ic}}{dt} = \frac{dV_a}{dt} + \frac{P_c - P_{ic}}{R_f} - \frac{P_{ic} - P_{vs}}{R_o} + I_i \quad \checkmark$$

$$C_{ic} = \frac{1}{k_E \cdot P_{ic}}$$

$$\frac{P_a - P_c}{R_a} = \frac{P_c - P_{ic}}{R_f} + \frac{P_c - P_{ic}}{R_{pv}}$$

$$V_a = C_a \cdot (P_a - P_{ic})$$

$$\frac{dV_a}{dt} = C_a \cdot \left(\frac{dP_a}{dt} - \frac{dP_{ic}}{dt}\right) + \frac{dC_a}{dt} \cdot (P_a - P_{ic}) \quad \checkmark$$

$$\frac{dC_a}{dt} = \frac{1}{\tau} \cdot [-C_a + \varsigma(G \cdot x)] \quad \checkmark$$

$$x = \frac{q - q_n}{q_n}$$

$$q = \frac{P_a - P_c}{R_a}$$

$$\varsigma(G \cdot x) = \frac{(C_{an} + \Delta C_a/2) + (C_{an} - \Delta C_a/2) \cdot \exp(G \cdot x/k_\varsigma)}{1 + \exp(G \cdot x/k_\varsigma)}$$

$$\begin{cases} \text{if } x < 0 \text{ then } \Delta C_a = \Delta C_{a1}; k_\varsigma = \Delta C_{a1}/4 \\ \text{if } x > 0 \text{ then } \Delta C_a = \Delta C_{a2}; k_\varsigma = \Delta C_{a2}/4 \end{cases}$$

$$R_a = \frac{k'_R}{r^4} = \frac{k_R \cdot C_{an}^2}{V_a^2}$$

3 coupled ODEs + algebraic equations

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	Value
Model parameters in hypothetical normal or basal condition	
R_o	526.3 mmHg · s · ml^{-1}
R_{pv}	1.24 mmHg · s · ml^{-1}
R_f	2.38 × 10^{3}mmHg · s · ml^{-1}
$\Delta C_{a\,1}$	0.75 ml/mmHg
$\Delta C_{a\,2}$	0.075 ml/mmHg
$C_{a\,n}$	0.15 ml/mmHg
k_E	0.11 ml^{-1}
k_R	4.91 × 10^{4}mmHg^{3} · s · ml^{-1}
τ	20 s
q_n	12.5 ml/s
G	1.5 ml · mmHg^{-1} · 100% CBF change^{-1}
Input quantities, pressure, and state variables in basal conditions	
P_a	100 mmHg
P_{ic}	9.5 mmHg
P_c	25 mmHg
P_{vs}	6.0 mmHg
C_a	0.15 ml/mmHg

11 parameters

Determined from patients and animal experiments

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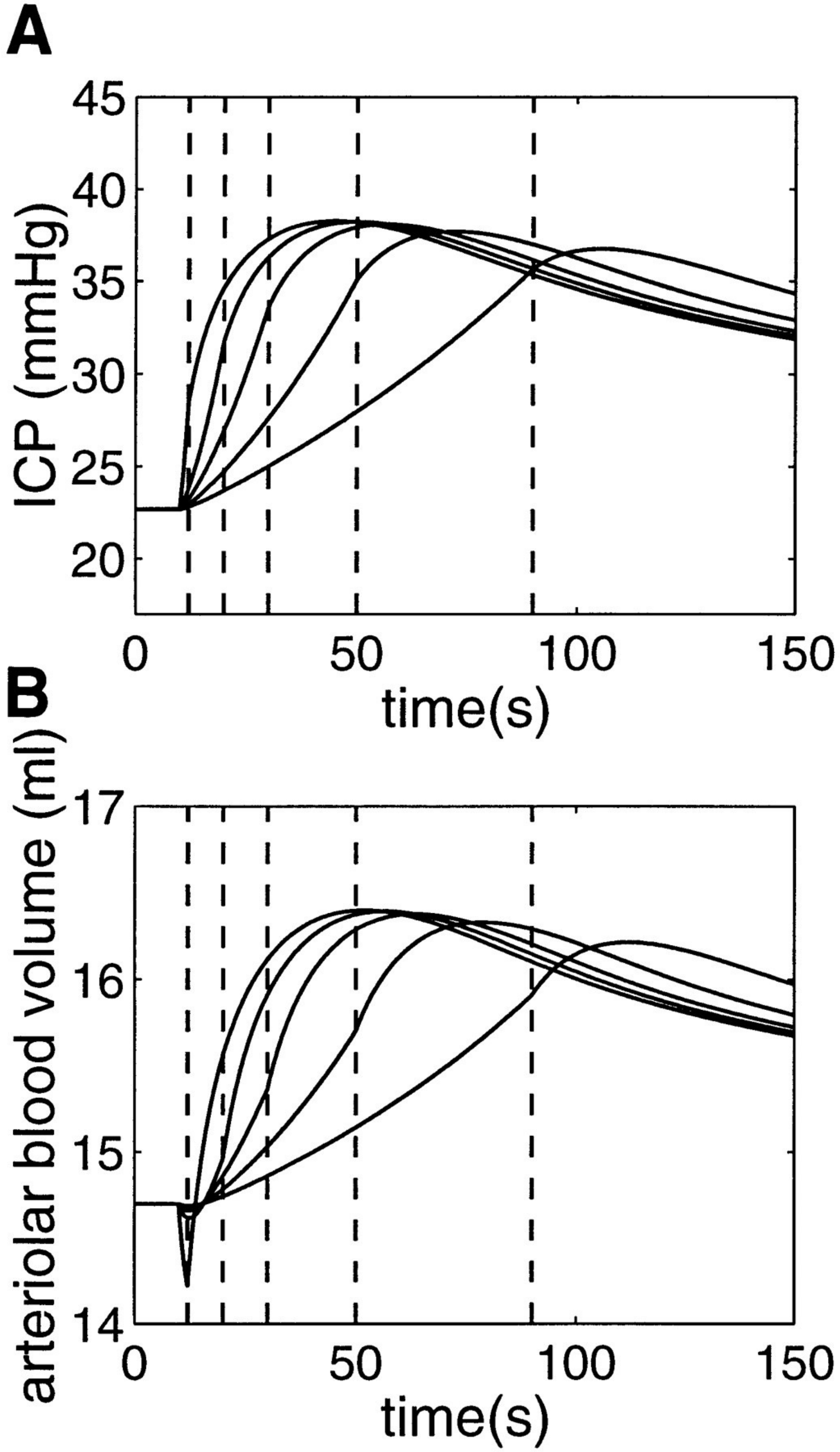


Pressure-Volume Index (PVI) test

- Inject bolus of saline into CSF space (lumbar puncture)
- 2 ml delivered over 2, 10, 20, 40, 80 Sec

Generic not personalized model
Personalization would require:

- measuring multiple signals, perhaps perturbations
- not clear how to perturb
- Choose 11 parameters via optimization of model response vs measured responses

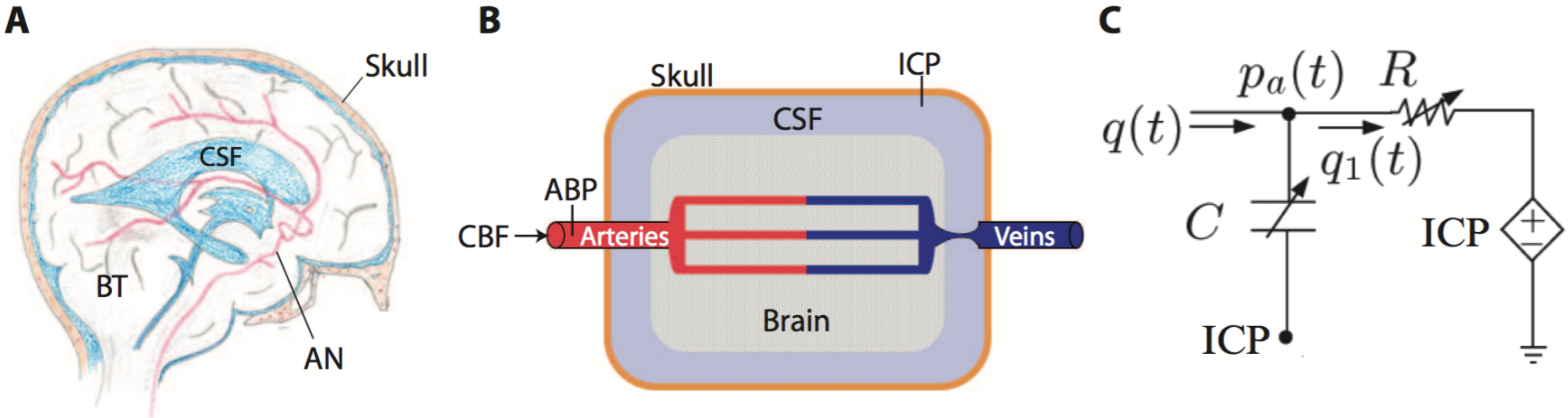


Fig. 1. Progressive abstraction of cerebrovascular physiology. (**A**) Relevant cerebrovascular anatomy: brain tissue (BT), cerebrospinal fluid (CSF), and cerebral arterial network (AN). (**B**) Schematic representation of the main cerebrovascular compartments and associated physiological variables: cerebral blood flow (CBF), arterial blood pressure (ABP), and intracranial pressure (ICP); the collapsed venous segment is also shown. (**C**) Lumped circuit-model representation of cerebrovascular physiology: CBF $q(t)$, cerebral arteriovenous flow $q_1(t)$, and ABP $p_a(t)$. ICP denotes both extraluminal pressure and the effective downstream pressure for cerebral perfusion.

- Cerebral Perfusion Pressure (CPP) = Mean arterial Pressure - Intracranial Pressure (ICP)
- CPP determines the “charge” that can be place on the cerebral arterial compliance (Q=CV)
- ICP establishes the downstream pressure rather than cerebral venous pressure and thus cerebral arteriovenous flow q_1(t) through arterial resistance R (middle cerebral artery)
- q(t) is cerebral blood flow

Applying Kirchoff's Current Law yields

$$q(t) = \frac{P_a(t) - ICP(t)}{R} + C\frac{d\left(P_a(t) - ICP(t)\right)}{dt}$$

Assume ICP varies slowly and is ~ constant over the analysis time window (some number of heart beats)

$$q(t) = \frac{P_a(t) - ICP}{R} + C\frac{dP_a(t)}{dt}$$

q(t) is a volume of blood per unit time. We can measure cerebral blood flow velocity (f(t)) in the middle cerebral artery (MCA) using ultrasound. Note

$$q(t) = f(t)\pi r^2$$

$$f(t) = \frac{P_a(t) - ICP}{R\pi r^2} + \frac{C}{\pi r^2}\frac{dP_a(t)}{dt} = \frac{P_a(t) - ICP}{R*} + C*\frac{dP_a(t)}{dt}$$

$$f(t) = \frac{P_a(t) - ICP}{R^*} + C^* \frac{dP_a(t)}{dt}$$

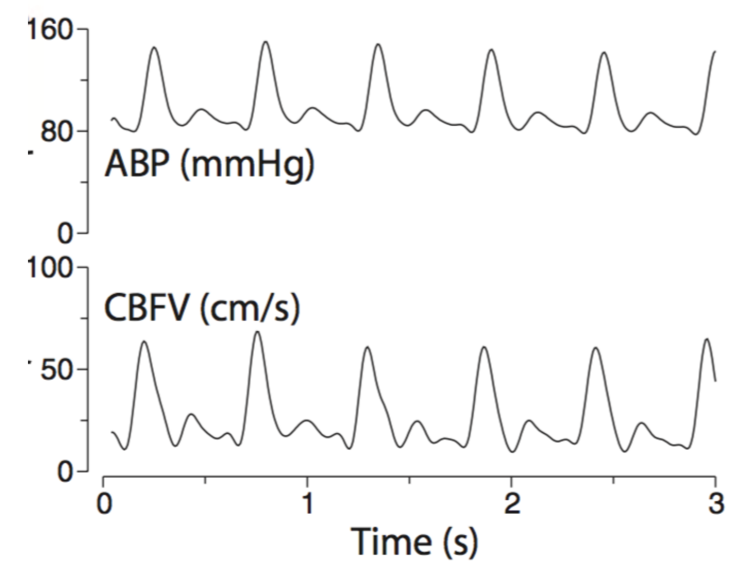
We can't measure arterial pressure in the MCA. We approximate it as that at the radial artery.

R* and C* are the unknowns.

Algorithm Step 1:

Let t_b and t_e be the beginning and end of the rapid systolic phase where heart contraction causes a rapid change in blood pressure. Over this time the capacitive current dominates so

$$f(t) \sim C^* \frac{dP_a(t)}{dt} \qquad t \in [t_b, t_e]$$



Therefore

$$\int_{t_b}^{t_e} f(t)\,dt = C^* \left[P_a(t_e) - P_a(t_b)\right] \Rightarrow C^* = \frac{\int_{t_b}^{t_e} f(t)\,dt}{\left[P_a(t_e) - P_a(t_b)\right]}$$

The problem with this approach is that there are errors in the integrated signal and measured pressures.

Therefore (as previously), do this over several beats and estimate $\hat{C}*$ as the least squares solution.

Algorithm Step 2:

We need to determine R (R*). Flow through R at any time t is $q_1(t)$

$$q_1(t) = q(t) - \hat{C}\frac{dP_a(t)}{dt} \Rightarrow \frac{q_1(t)}{\pi r^2} = \left[f(t) - \hat{C}*\frac{dP_a(t)}{dt} \right]$$

Approximate the derivative of the pressure waveform over successive time intervals

From the ckt model

$$ICP = P_a(t) - q_1(t)R = P_a(t) - \left[f(t) - \hat{C}*\frac{dP_a(t)}{dt} \right]\pi r^2 R = P_a(t) - \left[f(t) - \hat{C}*\frac{dP_a(t)}{dt} \right]R*$$

$$\frac{q_1(t)}{\pi r^2} = m(t) = \left[f(t) - \hat{C}*\frac{dP_a(t)}{dt} \right]$$

Measure m(t) at times t_1 and t_2 *within a single beat* thereby assuming ICP is constant, from the arterial pressure and ultrasound measurements. This yields

$$P_a(t_1) - P_a(t_2) = R^*\left(m(t_1) - m(t_2)\right)$$

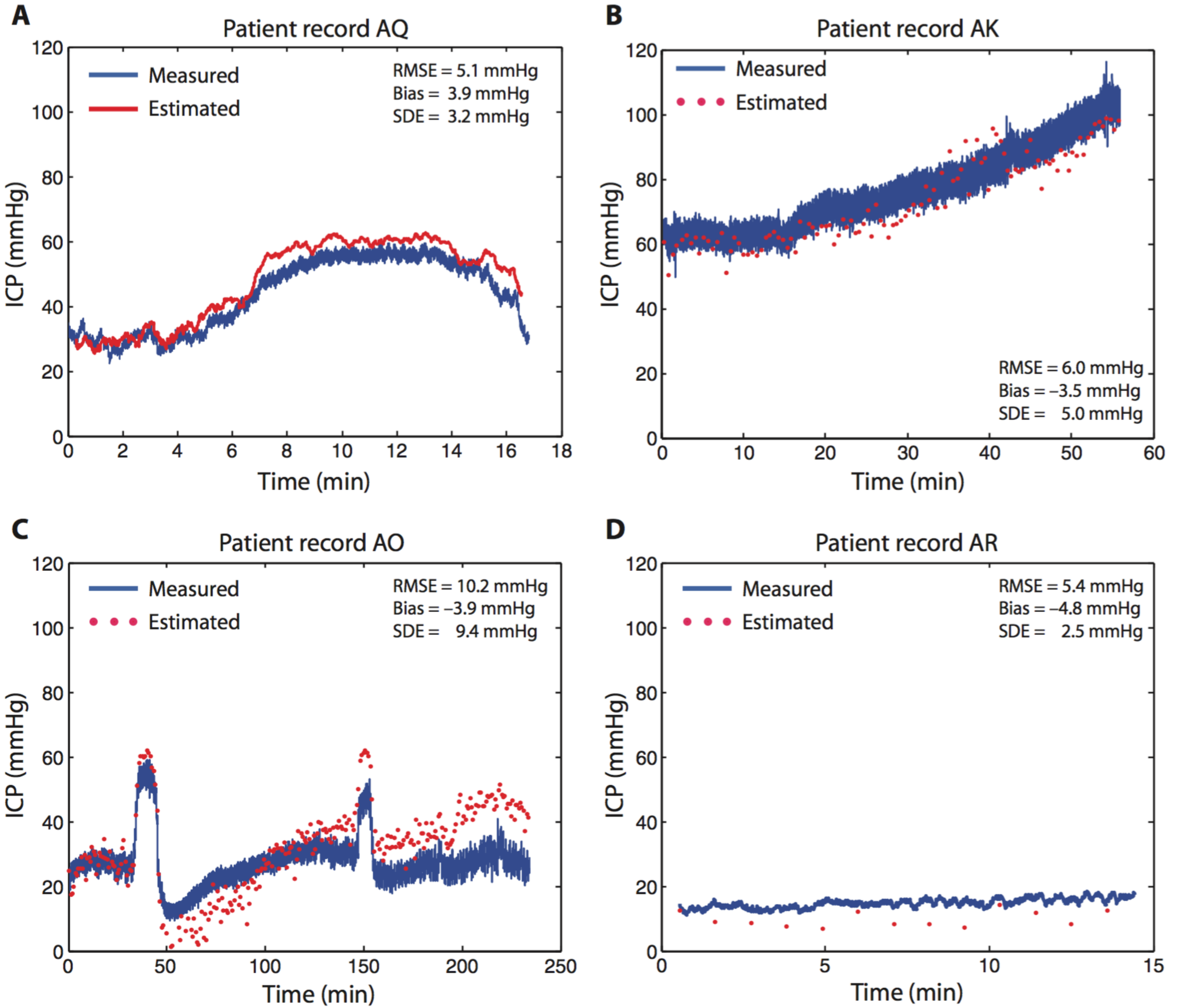
Do the least squares thing again over several beats to get $\hat{R}^*$.

Finally

$$IC\hat{P} = \overline{P}_a(t) - \hat{R}^*\,\overline{m}(t)$$

The "bar" symbols denote averages of measured quantities over the observation window

Derivation differs from that in the paper to emphasize that the scale factor due to measurement of blood flow velocity rather than blood flow doesn't matter


A
Patient record AQ
Measured
Estimated
RMSE = 5.1 mmHg
Bias = 3.9 mmHg
SDE = 3.2 mmHg
ICP (mmHg)
Time (min)
B
Patient record AK
Measured
Estimated
RMSE = 6.0 mmHg
Bias = –3.5 mmHg
SDE = 5.0 mmHg
ICP (mmHg)
Time (min)
C
Patient record AO
Measured
Estimated
RMSE = 10.2 mmHg
Bias = –3.9 mmHg
SDE = 9.4 mmHg
ICP (mmHg)
Time (min)
D
Patient record AR
Measured
Estimated
RMSE = 5.4 mmHg
Bias = –4.8 mmHg
SDE = 2.5 mmHg
ICP (mmHg)
Time (min)