Intracranial pressure elevation alters CSF clearance pathways

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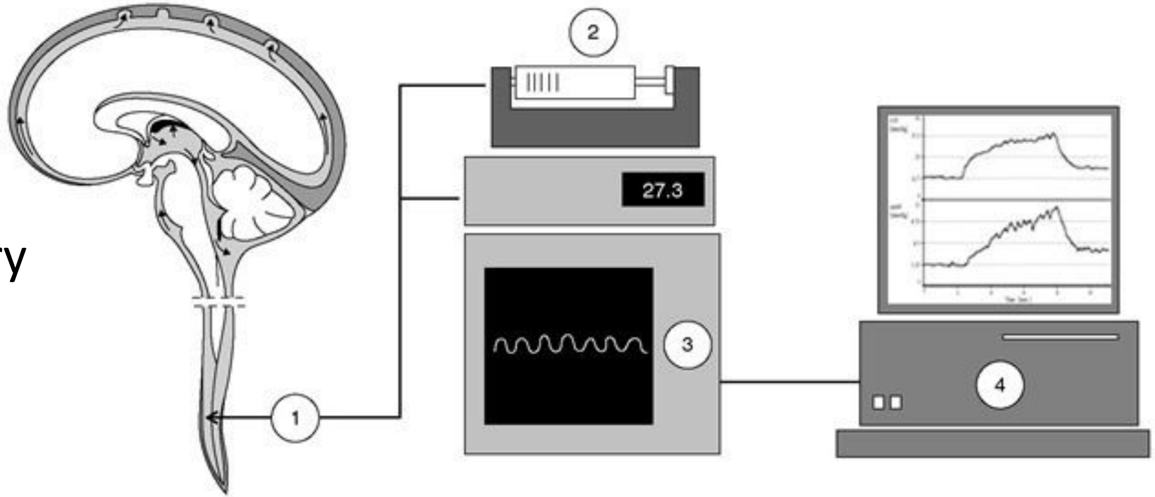
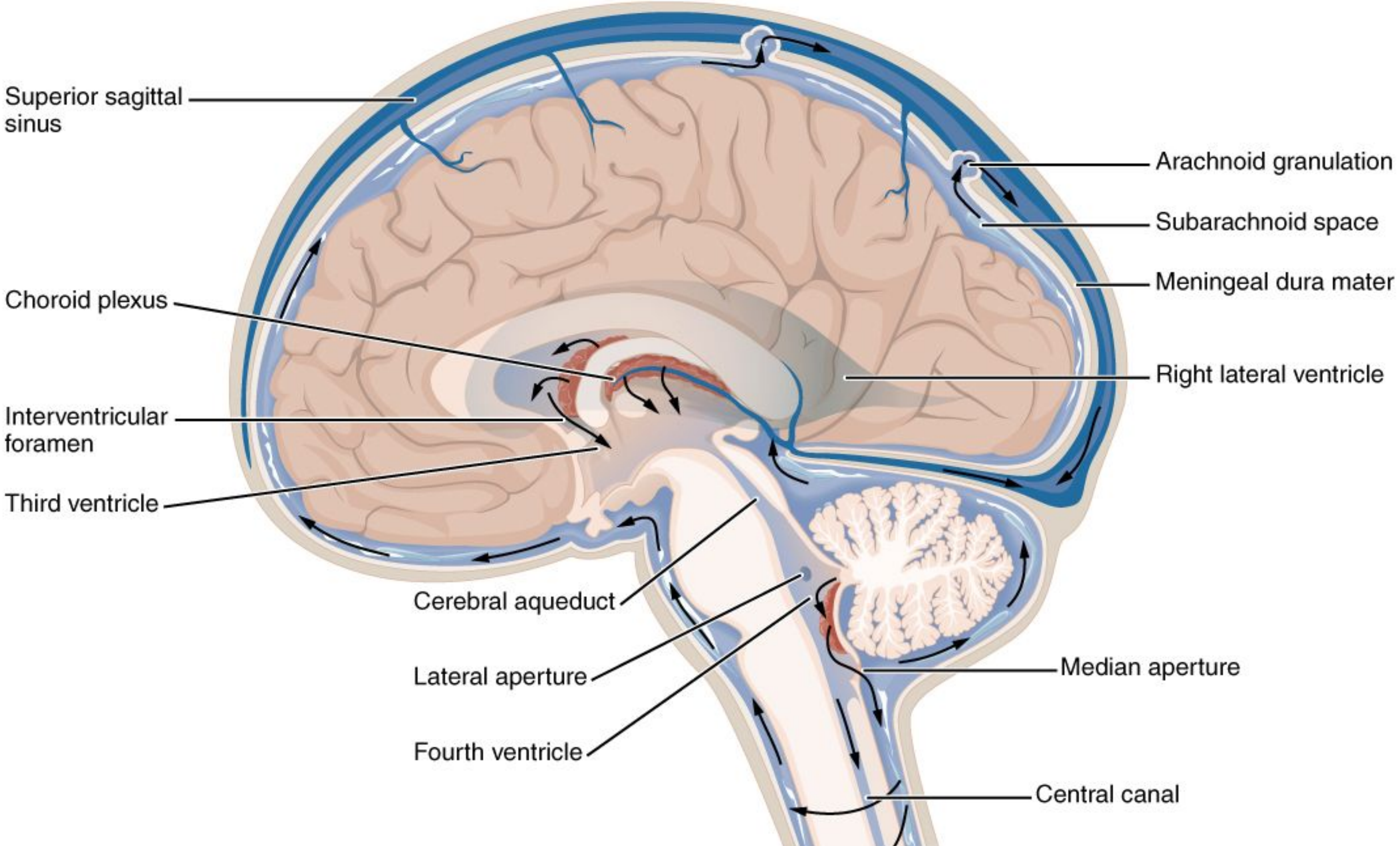
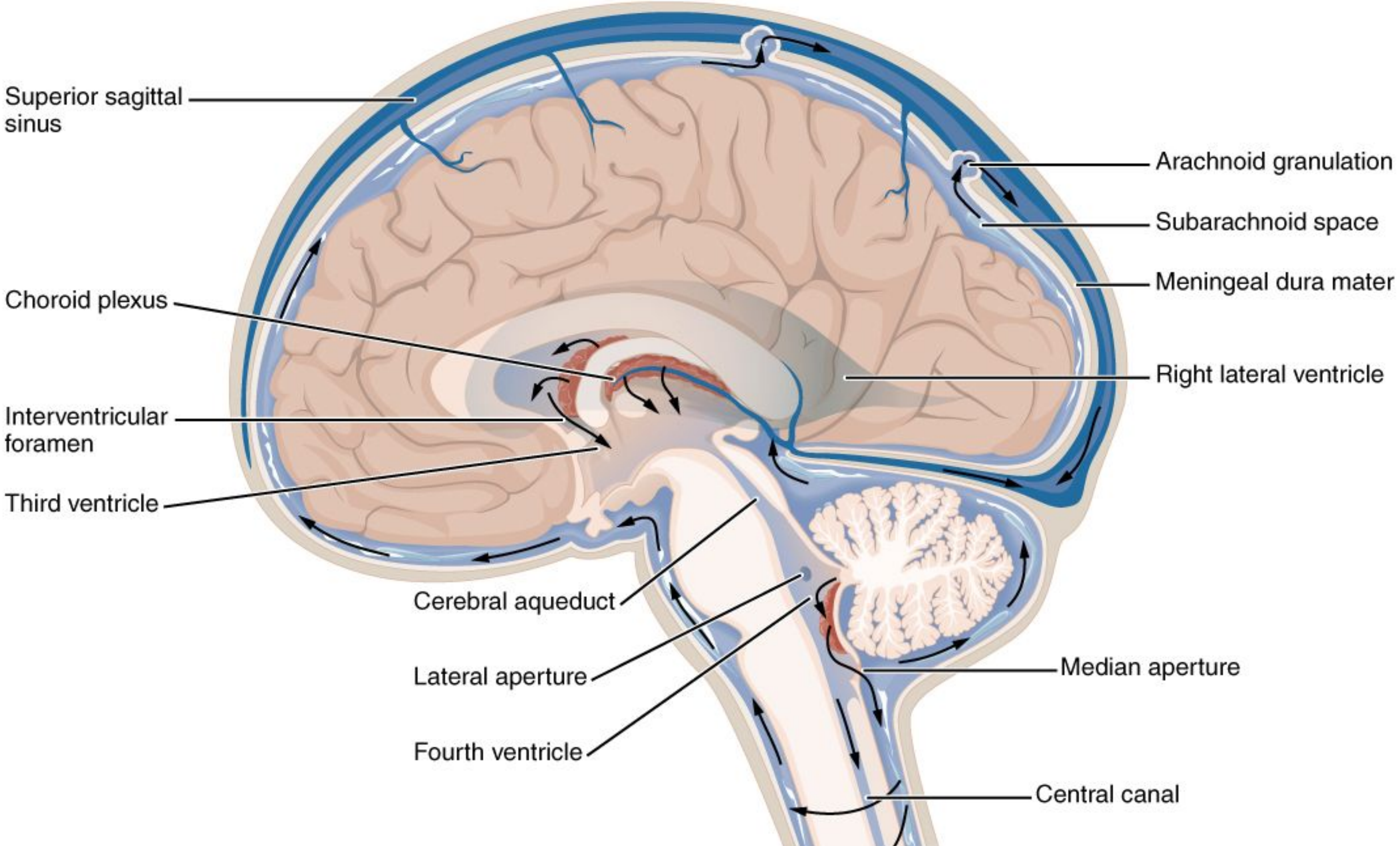


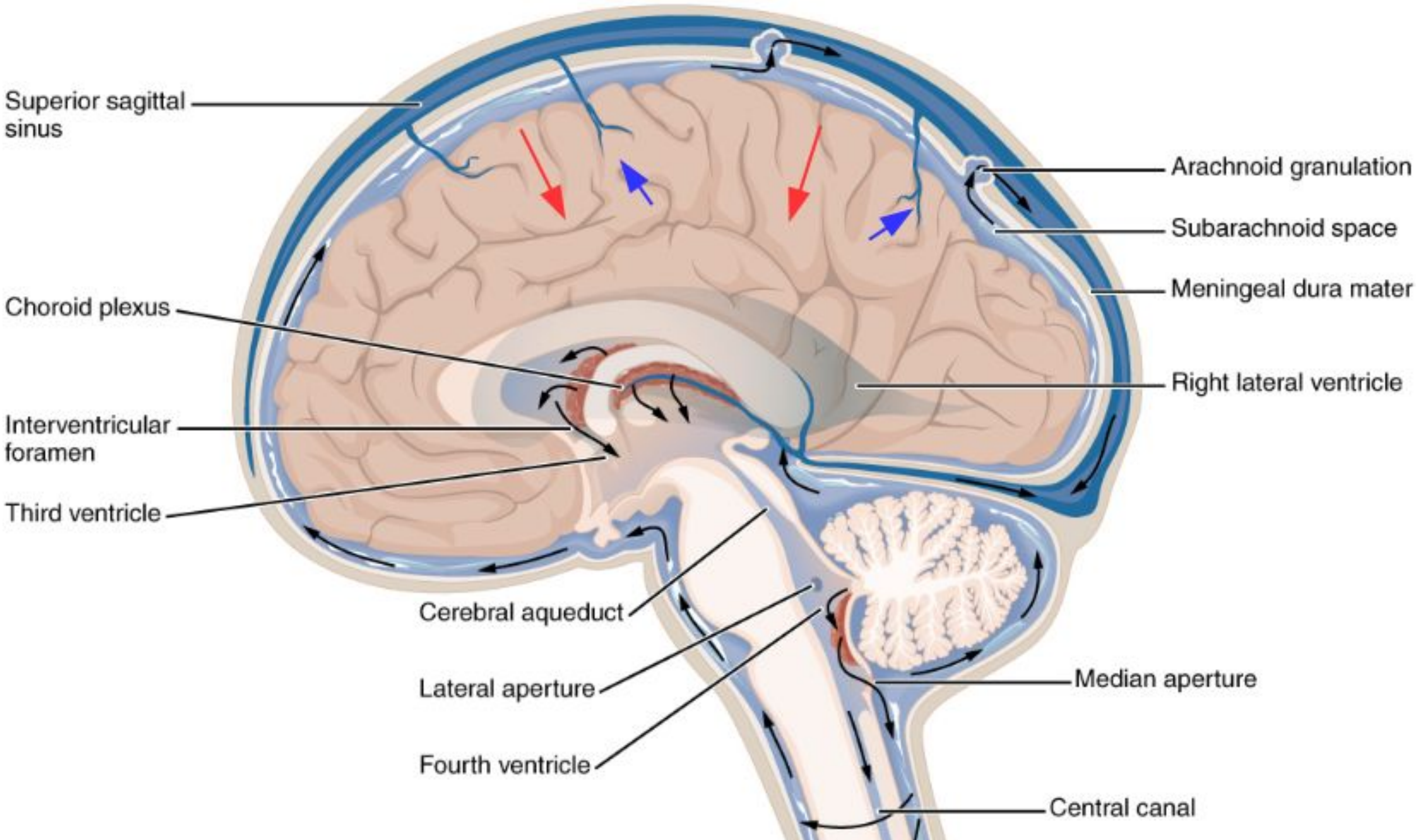
CSF flows from the choroid plexus to the arachnoid granulations



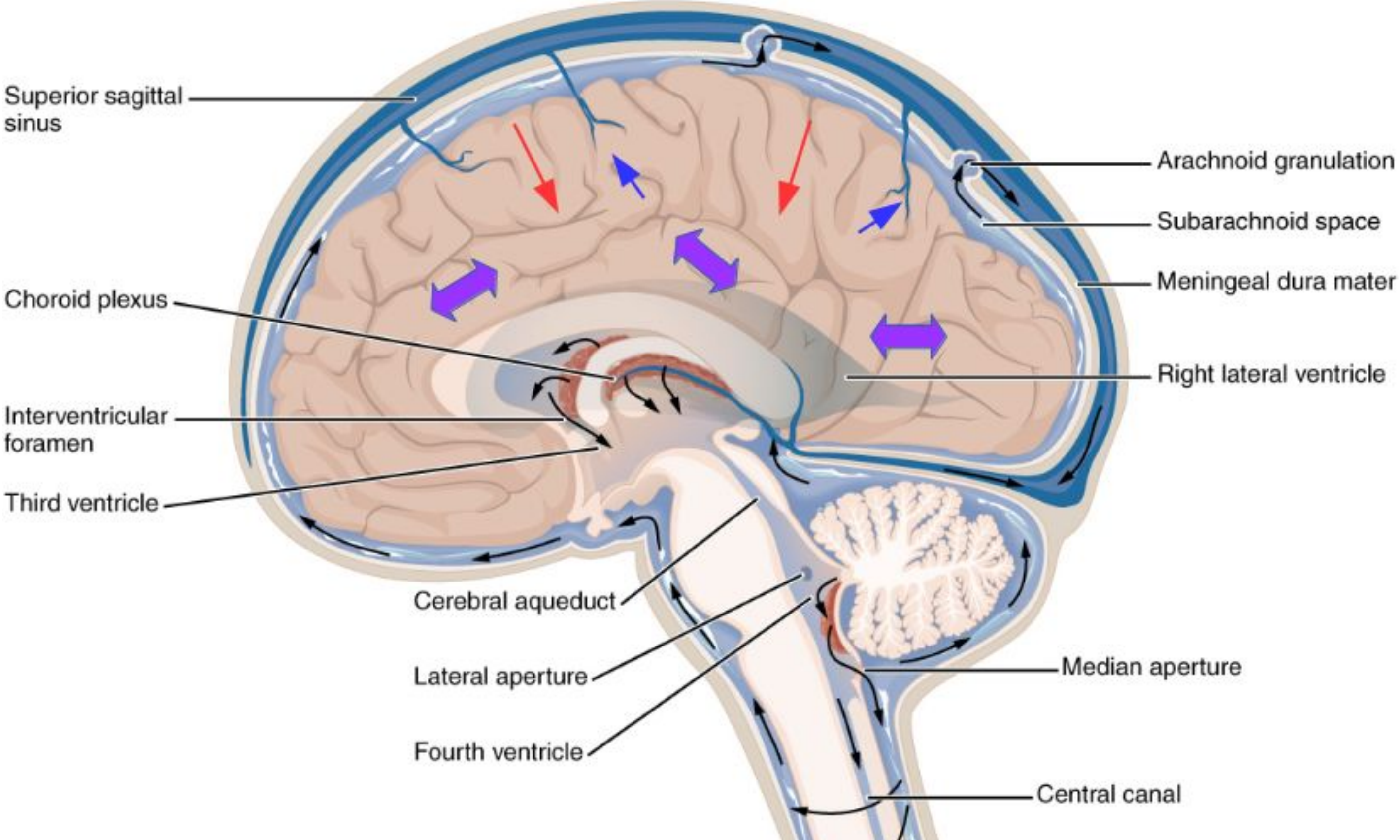
CSF flows from the choroid plexus to the arachnoid granulations, but not exclusively



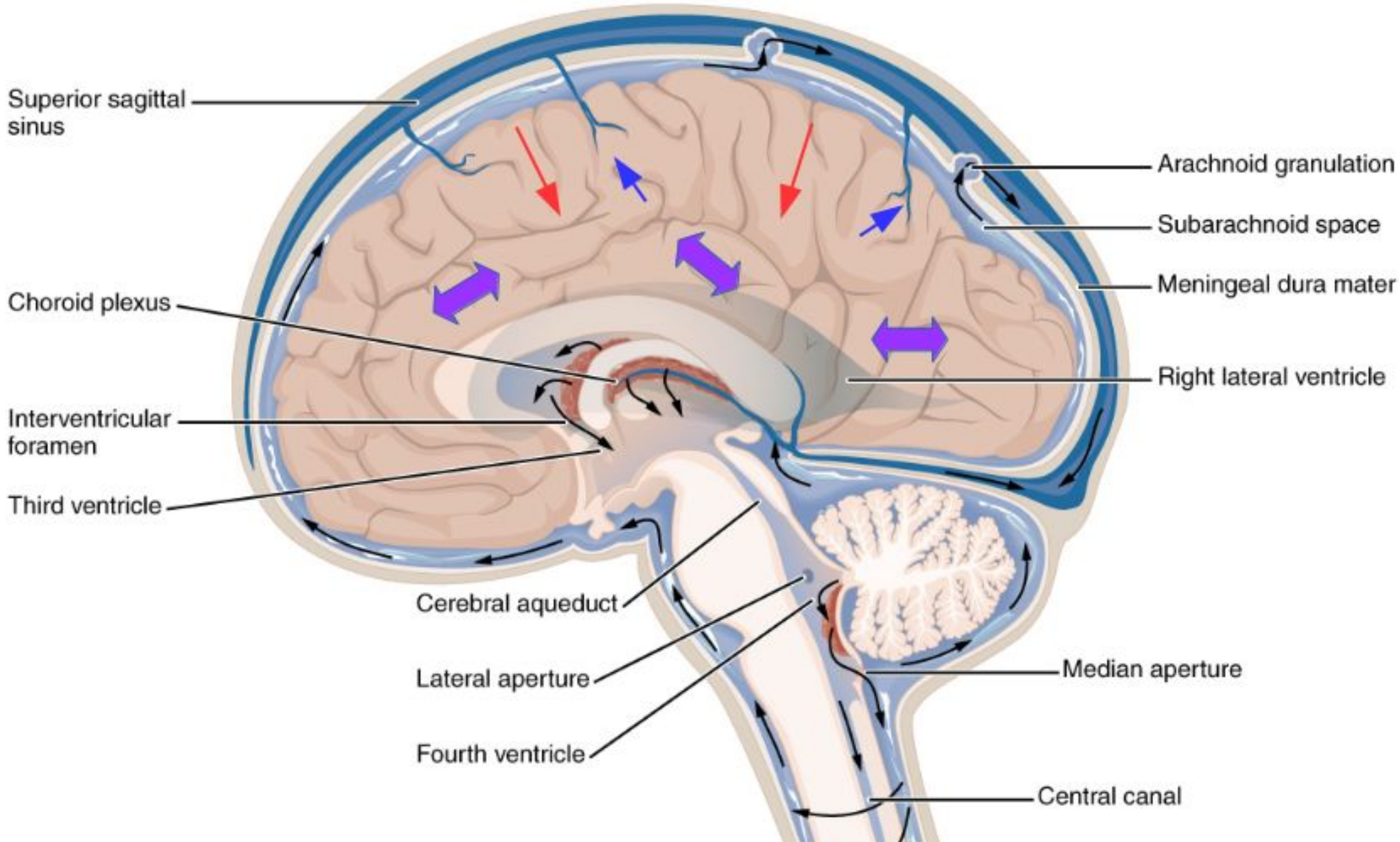
CSF may enter paravascular spaces



CSF may enter paravascular spaces, and water may be filtrated over the capillary wall



In addition, cardiac and respiratory effects add pulsatility to CSF flow



Respiratory influence on cerebrospinal fluid flow – a computational study based on long-term intracranial pressure measurements

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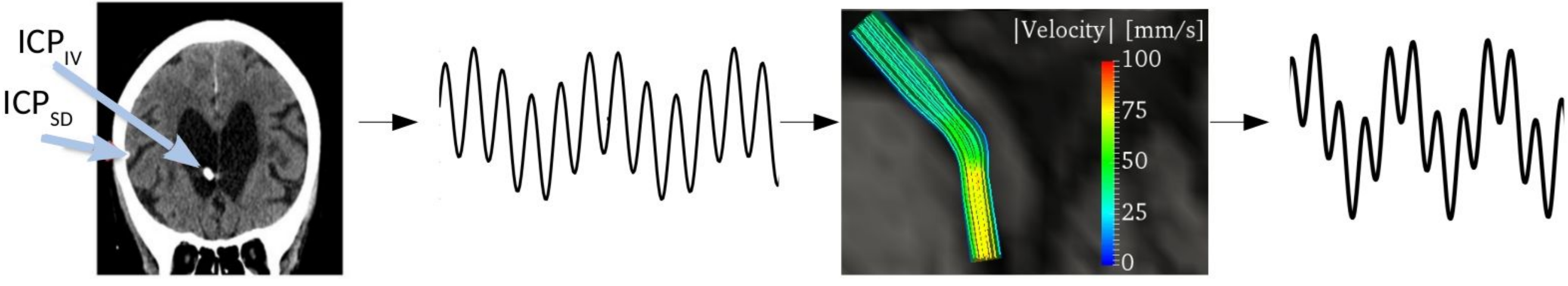
Respiration may affect CSF flow despite inducing a smaller pressure gradient than the cardiac component



Long term ICP measurements

Simplified intracranial pressure gradient waveforms

CSF flow model

Respiratory and cardiac components of aqueductal flow

Respiration may affect CSF flow despite inducing a smaller pressure gradient than the cardiac component

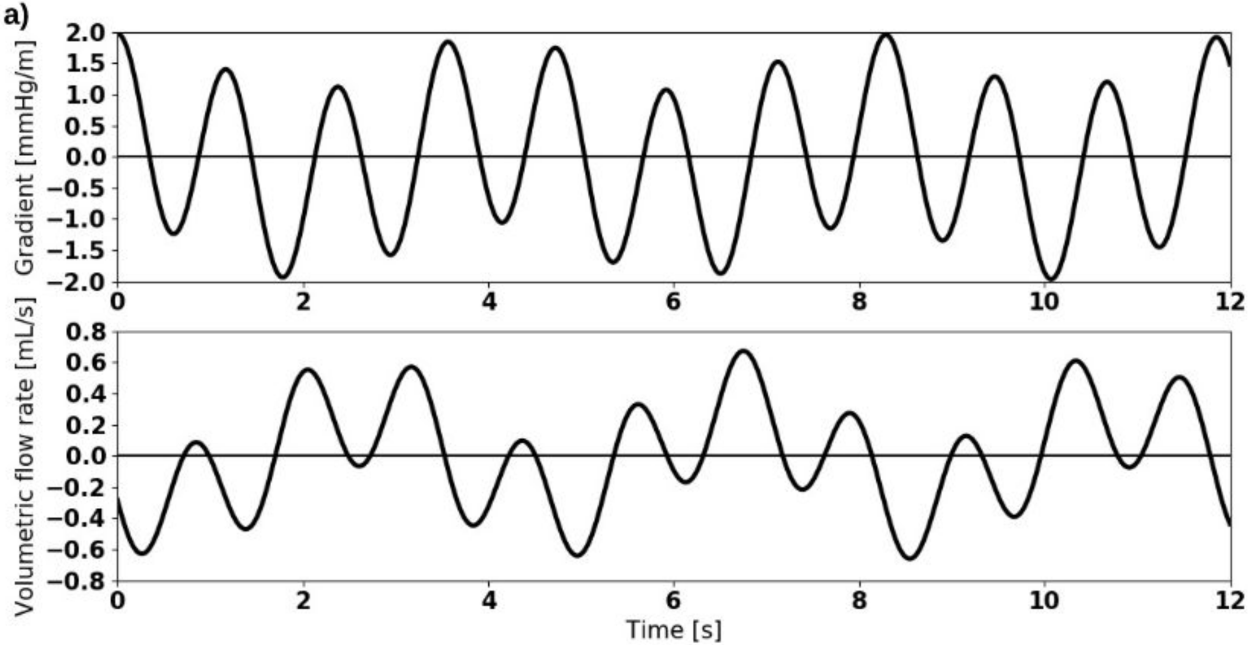


Figure: Example of a patient's simplified pressure gradient and the corresponding computed flow rate

Respiration may affect CSF flow despite inducing a smaller pressure gradient than the cardiac component

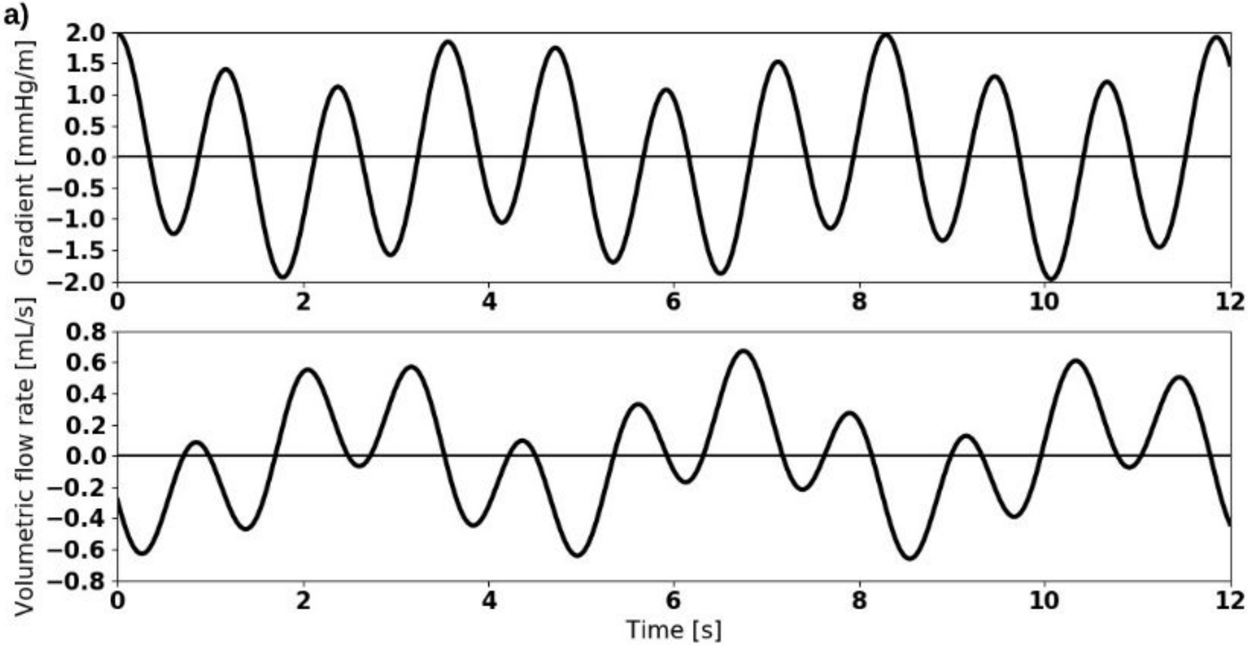


Figure: Example of a patient’s simplified pressure gradient and the corresponding computed flow rate

Cohort Average

Cardiac: 1.46 mmHg/m

Respiratory: 0.52 mmHg/m

Cardiac: 0.31 mL/sec

Respiratory: 0.35 mL/sec

Respiration may affect CSF flow despite inducing a smaller pressure gradient than the cardiac component

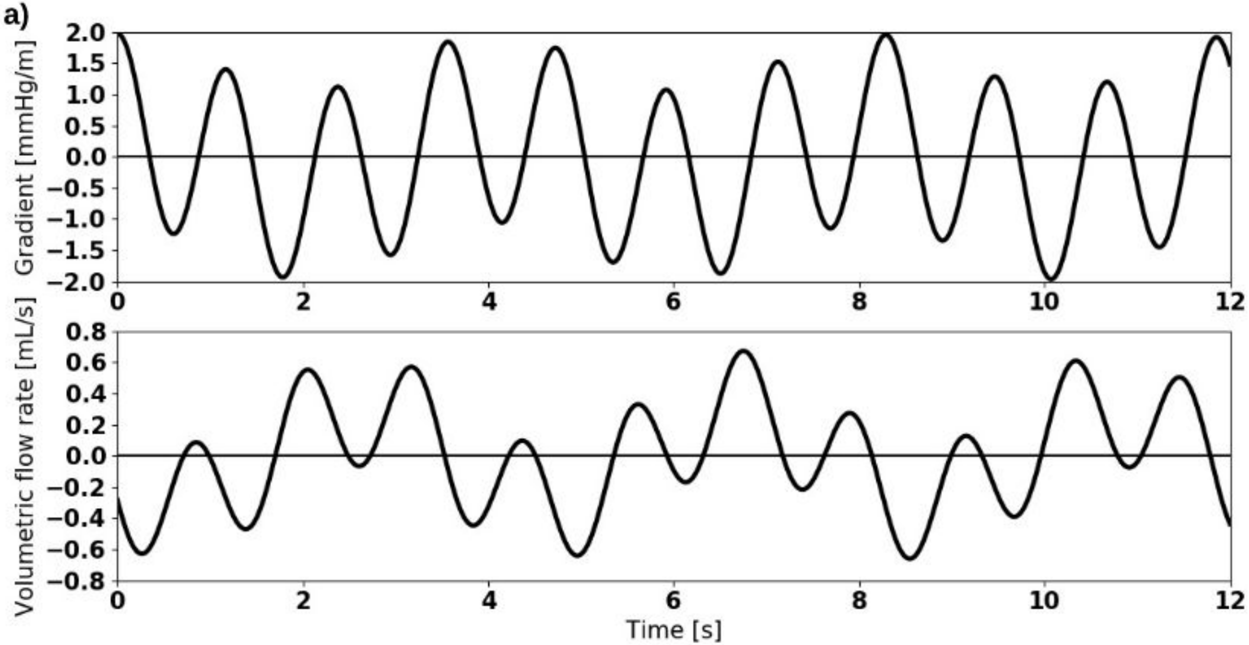


Figure: Example of a patient's simplified pressure gradient and the corresponding computed flow rate

Cohort Average

Cardiac: 1.46 mmHg/m

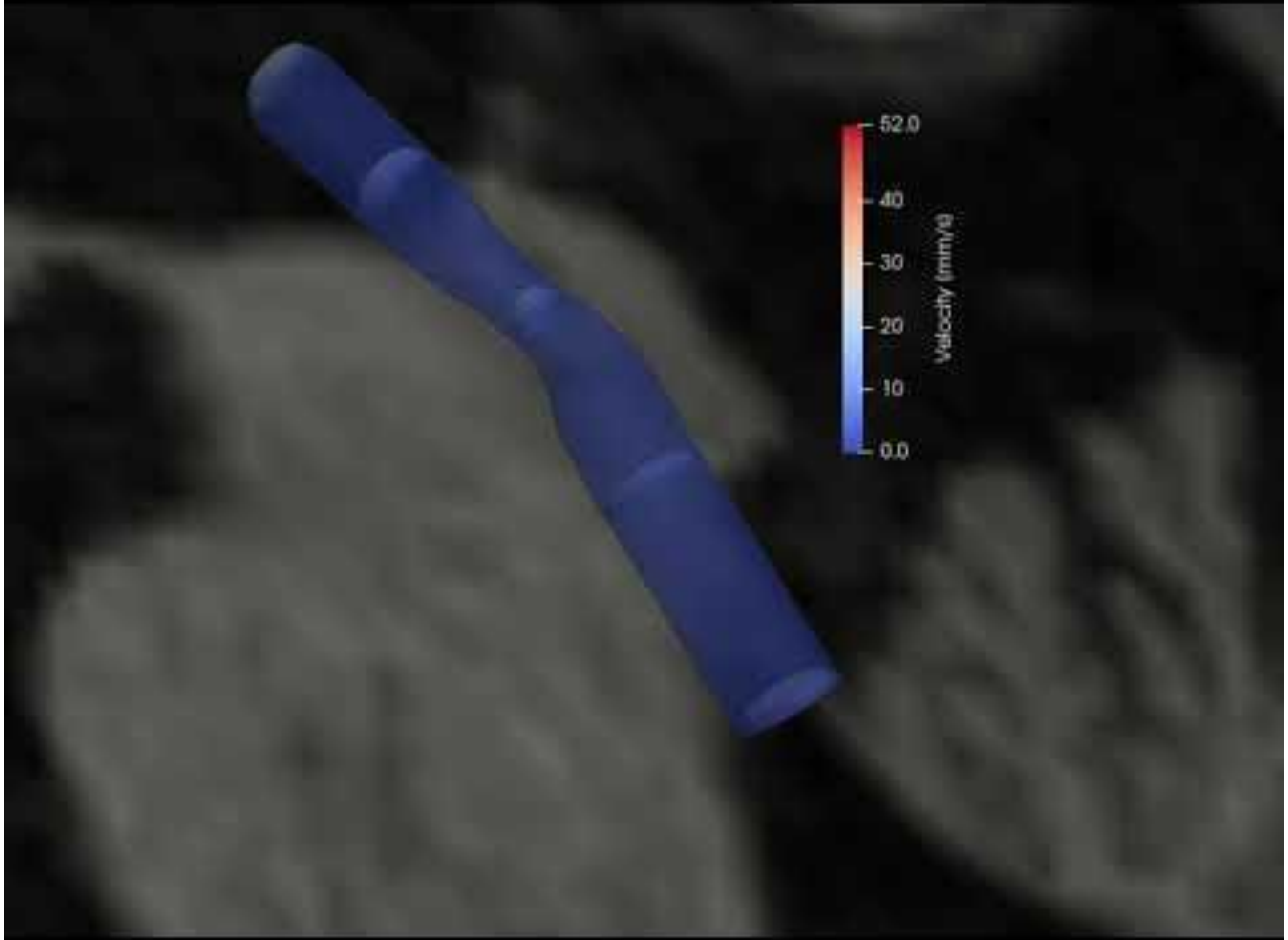
Respiratory: 0.52 mmHg/m

Static: ~0.005 mmHg/m

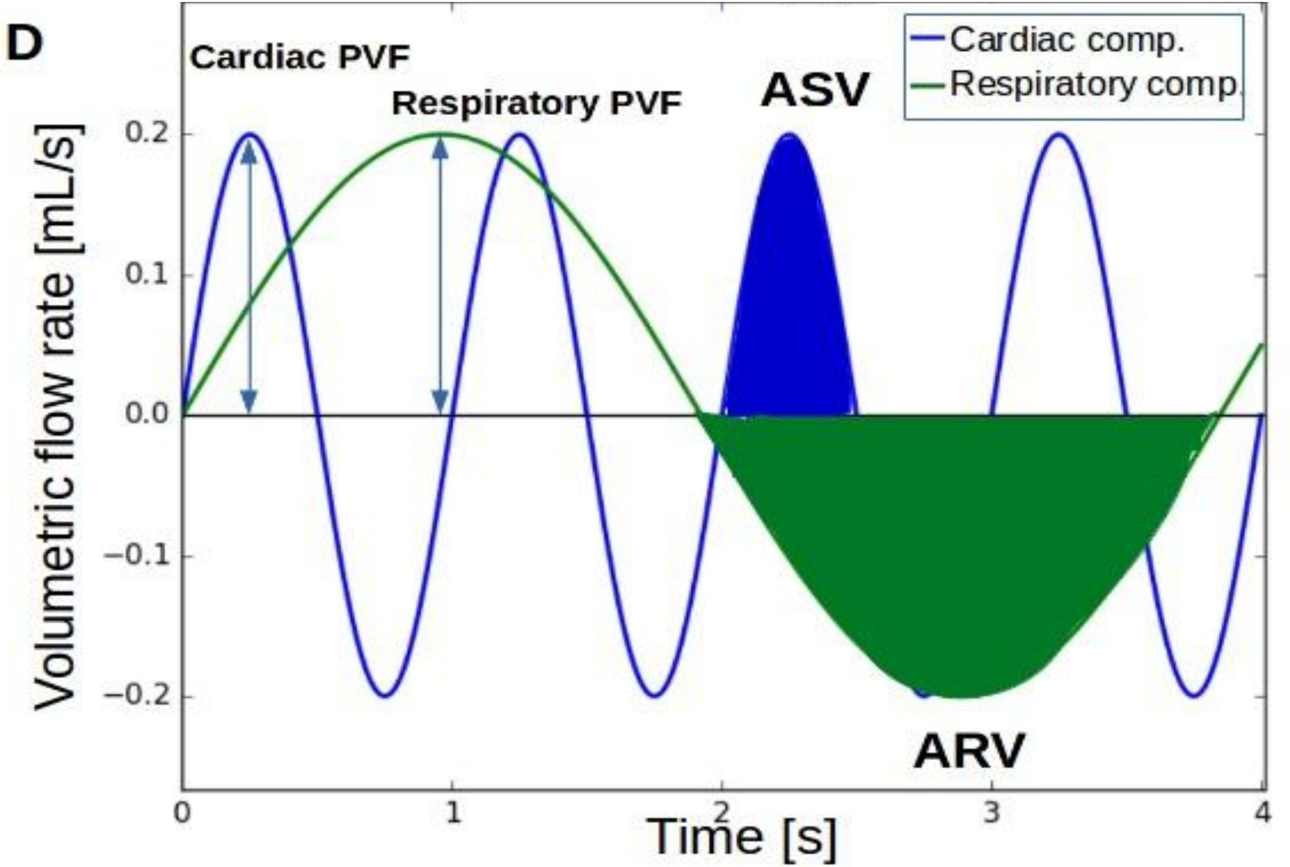
Cardiac: 0.31 mL/sec

Respiratory: 0.35 mL/sec

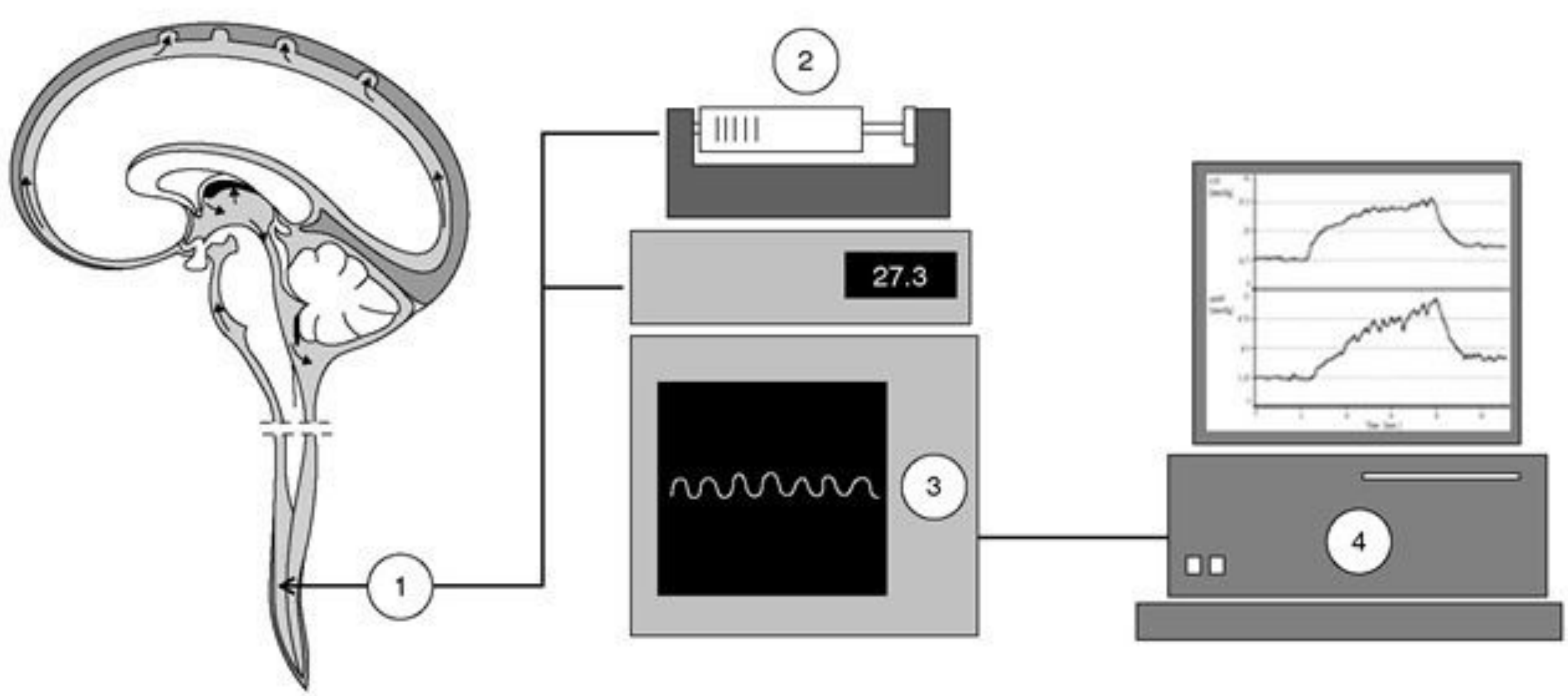
Static: ~0.006 mL/sec


52.0
40
30
20
10
0.0
Velocity (mm/s)

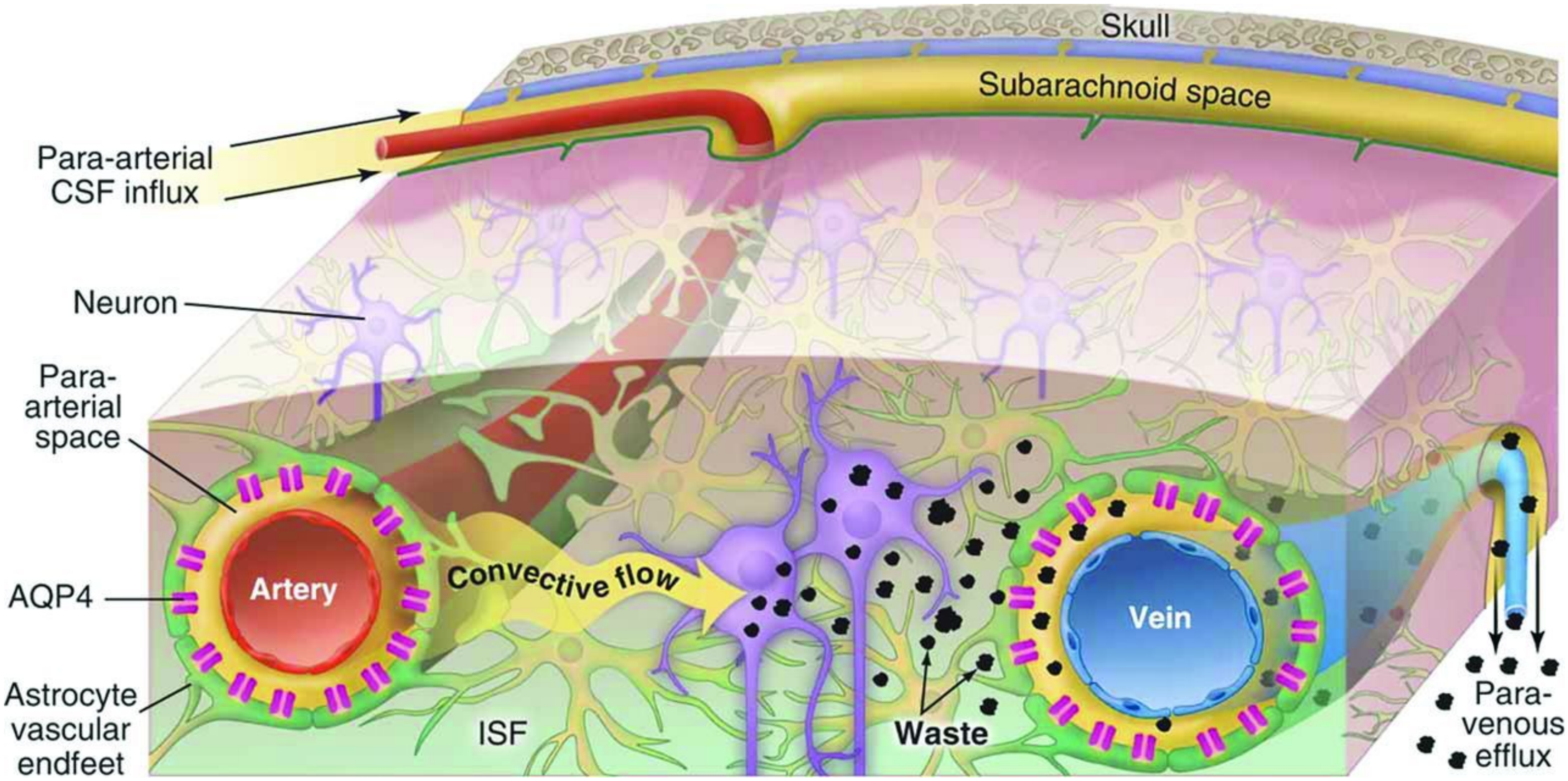
The long respiratory wave carry a greater volume than the shorter cardiac wave



During infusion, a long/static ICP wave is induced by fluid injection, resulting in a pressure increase of 10 - 25 mmHg

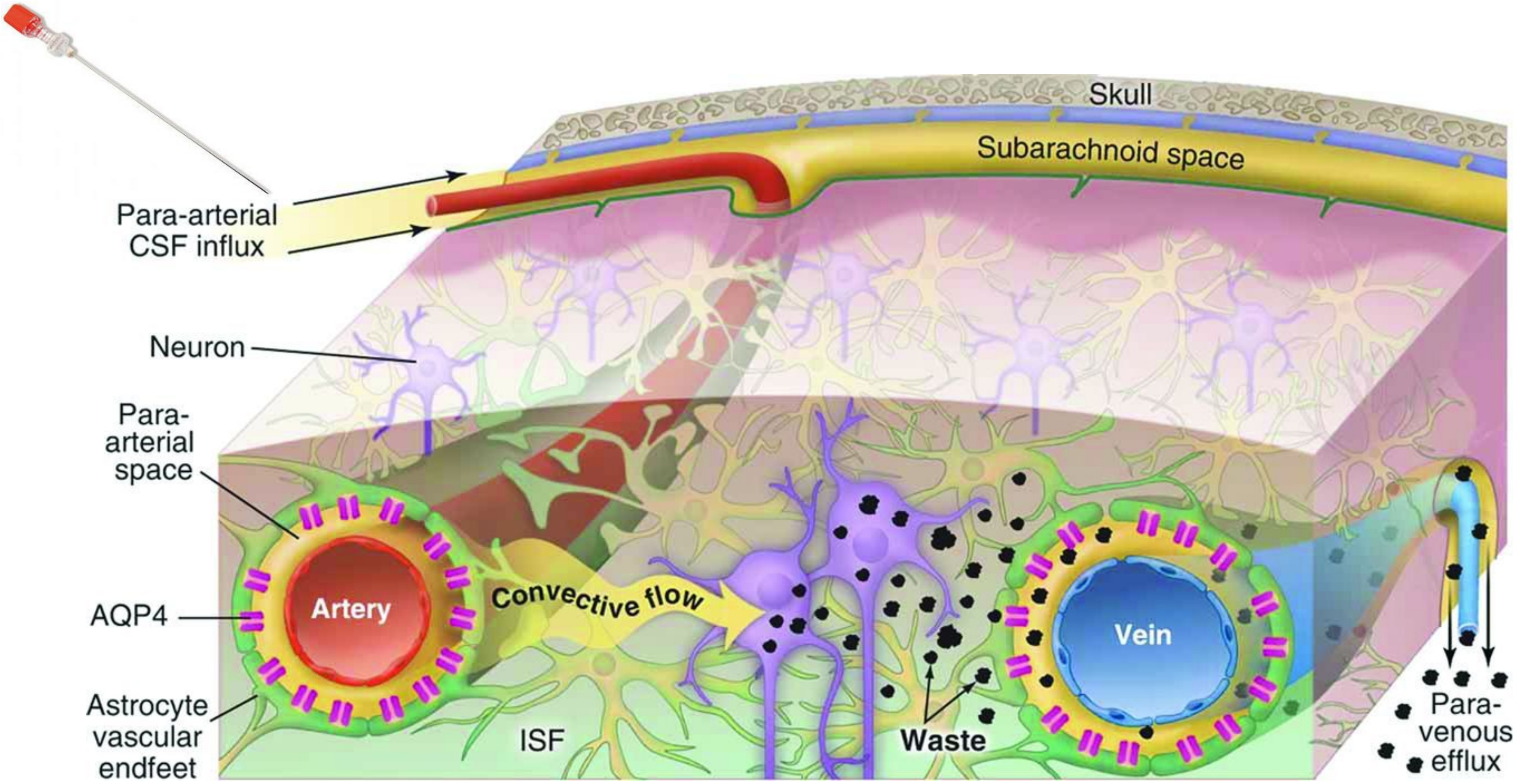


The glymphatic system has been proposed to be driven by arterial pulsations, and possibly respiratory effects



Mestre et al. 2017

However, in some studies of the glymphatic system, infusion rates has caused pressure increase of several mmHg



Mestre et al. 2017

In our study, we explored the link between infusion and the glymphatic system

Intracranial pressure elevation alters CSF clearance pathways

Vegard Vinje[1,*], Karen-Helene Støverud[2], Marie E. Rognes[1], Anders Eklund[2], and Kent-Andre Mardal[1,3]

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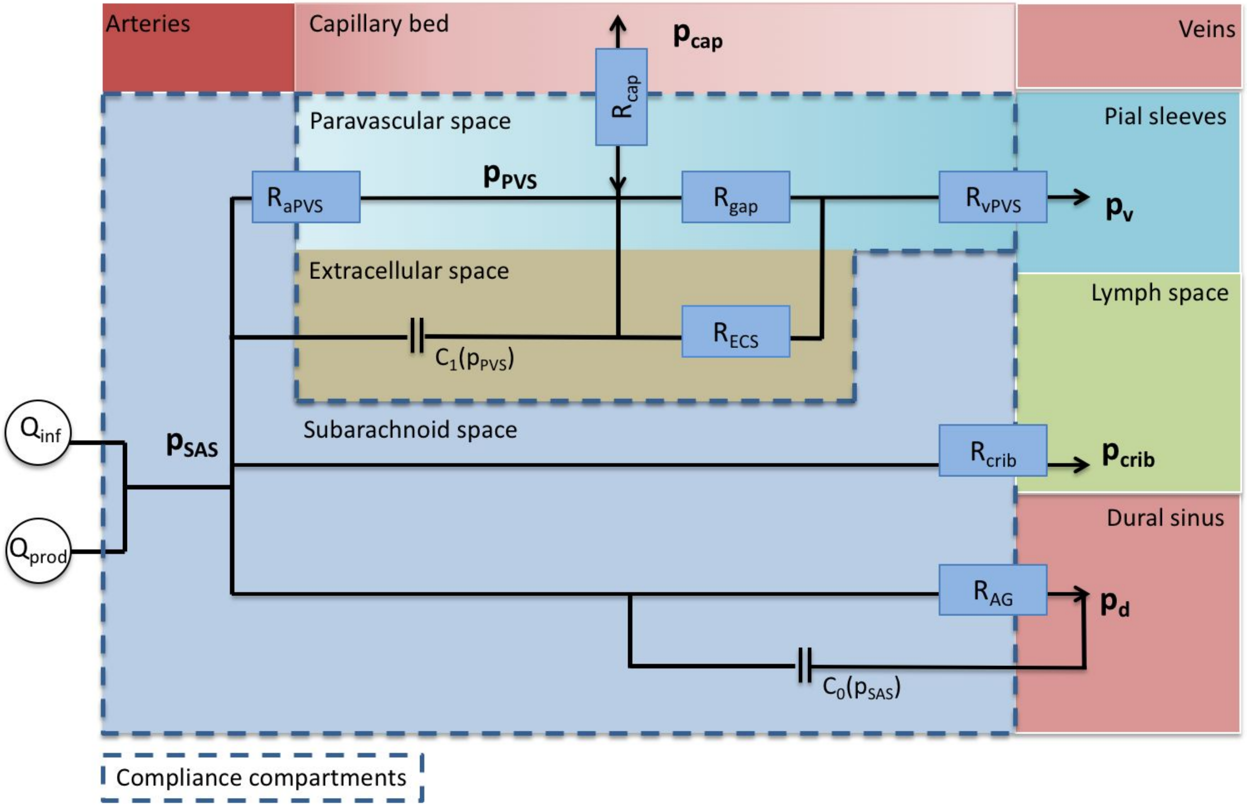
In our study, we explored the link between infusion and the glymphatic system

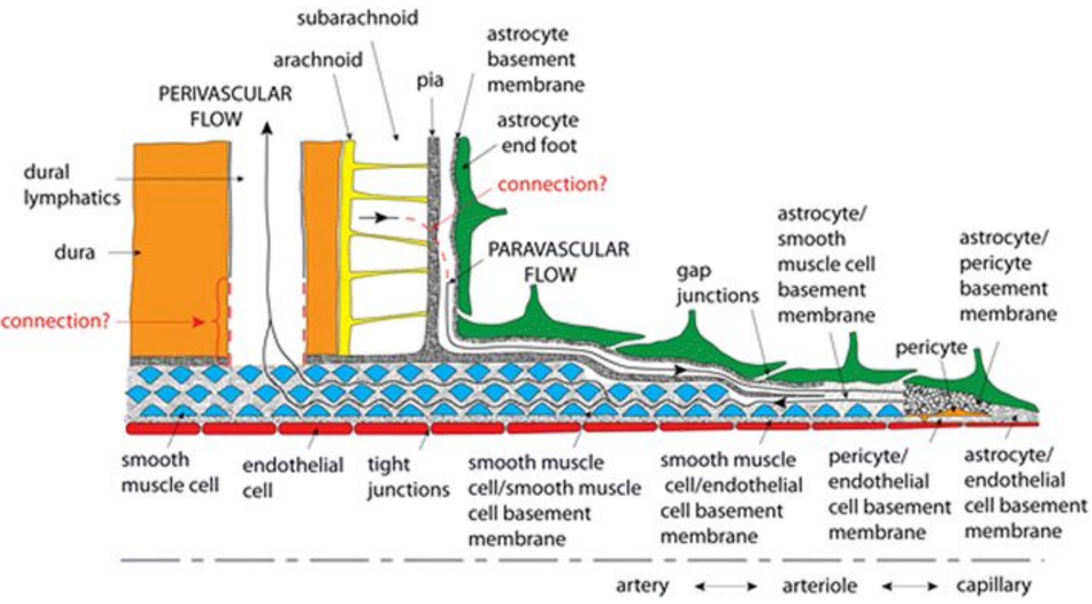


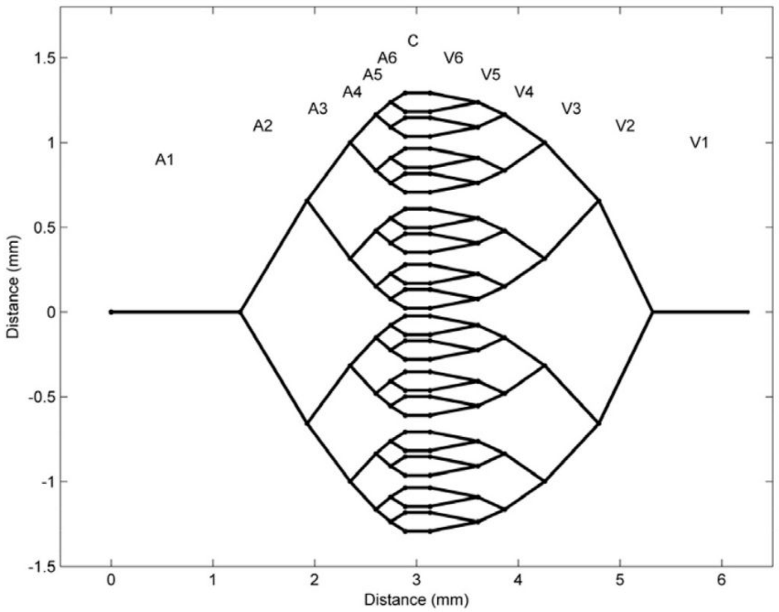
By modeling the ICP pressure in the SAS (p_0) and in the paravascular space (p_1), flow can be computed between the two compartments

$$C_0(p_0)\frac{\partial p_0}{\partial t} = Q_{\text{in}} + \frac{1}{R_{\text{AG}}}(p_{\text{d}} - p_0) + \frac{1}{R_{\text{crib}}}(p_{\text{crib}} - p_0) + \frac{1}{R_{\text{aPVS}}}(p_1 - p_0), \quad (1)$$

$$C_1(p_1)\frac{\partial p_1}{\partial t} = \frac{1}{R_{\text{V}}}(p_{\text{V}} - p_1) + \frac{1}{R_{\text{cap}}}(p_{\text{cap}} - p_1) + \frac{1}{R_{\text{aPVS}}}(p_0 - p_1). \quad (2)$$

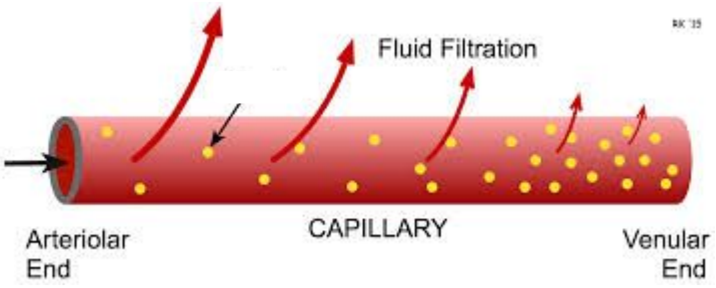
Resistances not found in the literature were calculated based on previous studies[1,2]





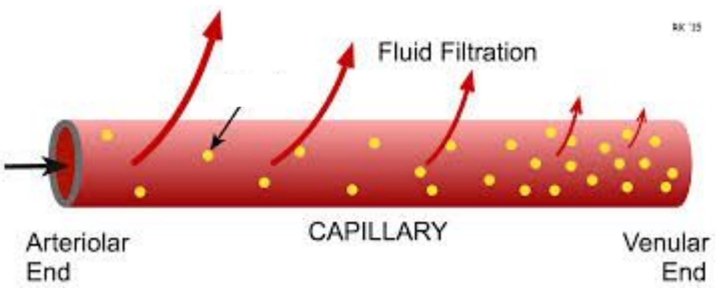
1. Faghih and Sharp, 2018
2. Payne and El-Bouri, 2018

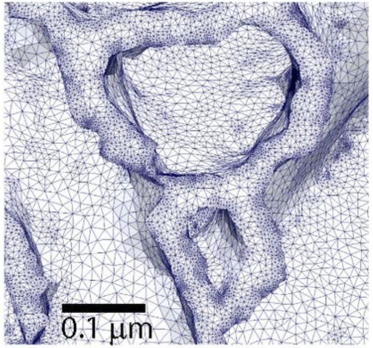
Calculated resistances were found at the same order of magnitude as other outflow resistances found experimentally



R_{Cap} = 125 mmHg/(mL/min)

Calculated resistances were found at the same order of magnitude as other outflow resistances found experimentally

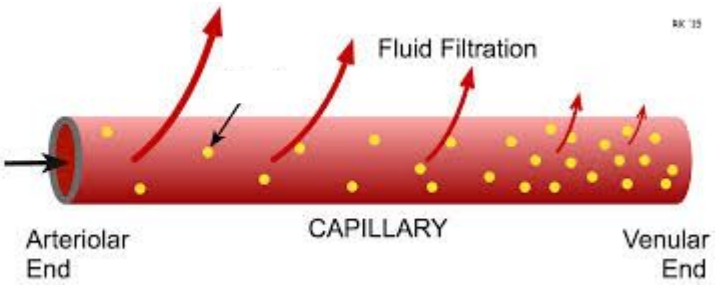


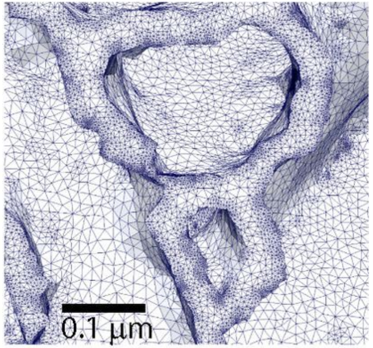


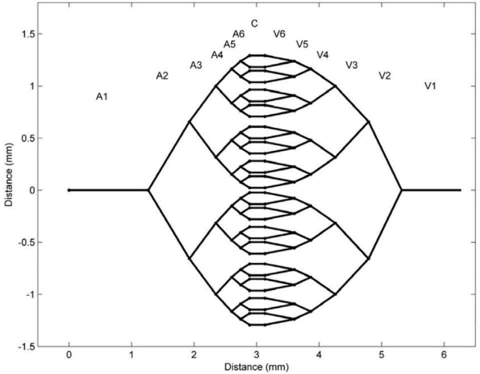
R_{Cap} = 125 mmHg/(mL/min)

R_{ECS} = 80 mmHg/(mL/min)

Calculated resistances were found at the same order of magnitude as other outflow resistances found experimentally



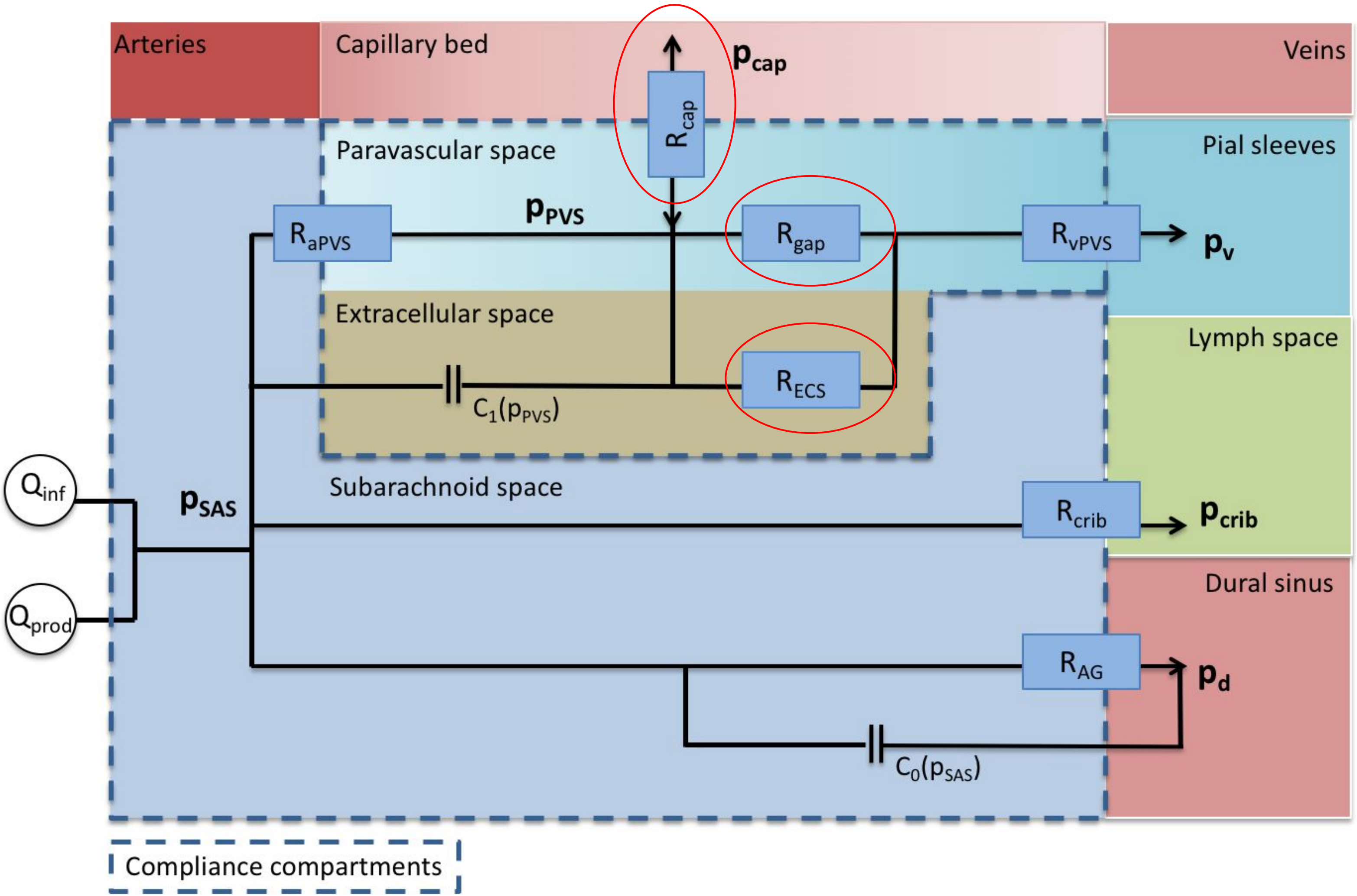




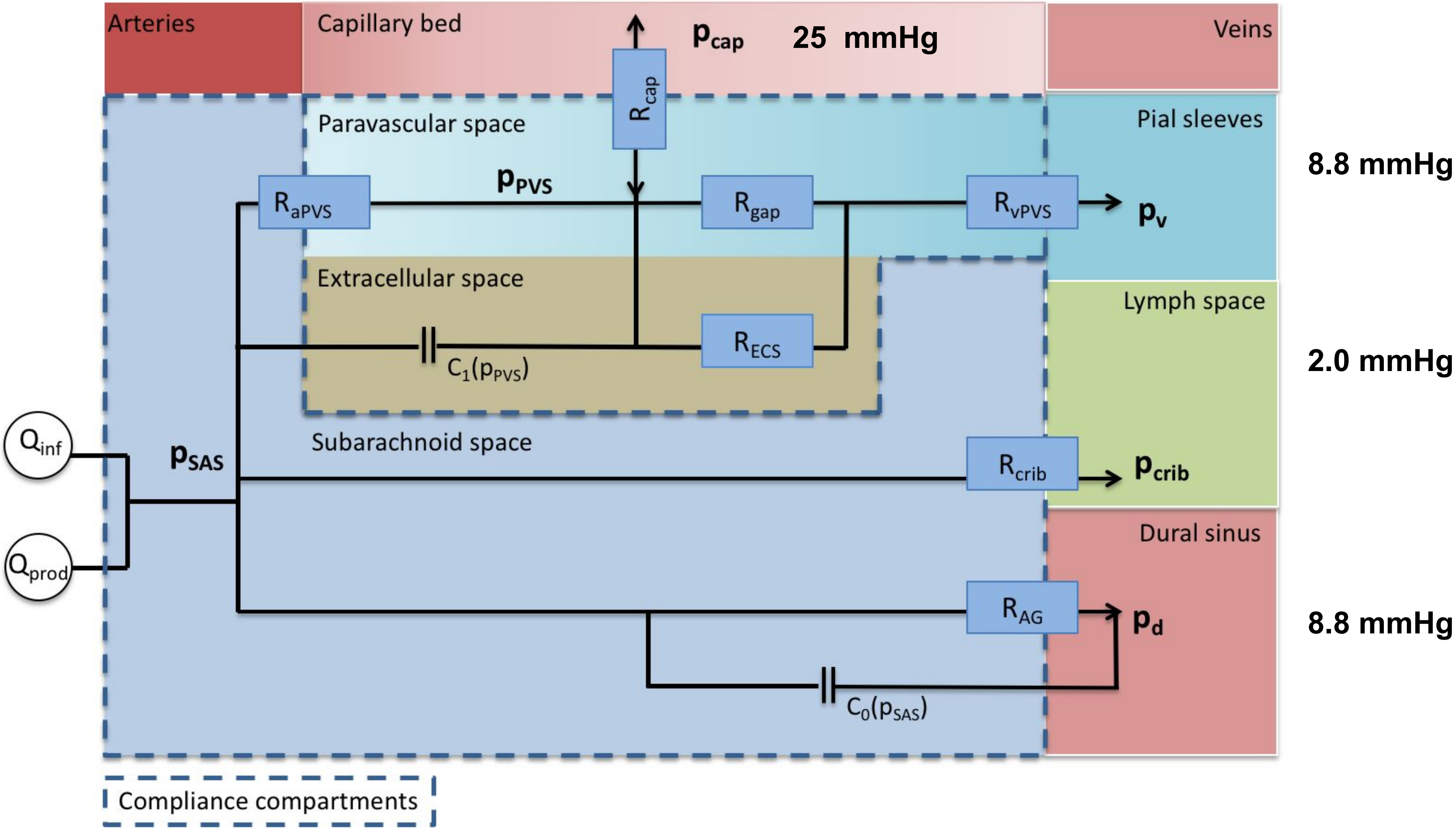
R_{Cap} = 125 mmHg/(mL/min)

R_{ECS} = 80 mmHg/(mL/min)

R_{gaps} = 32 mmHg/(mL/min)

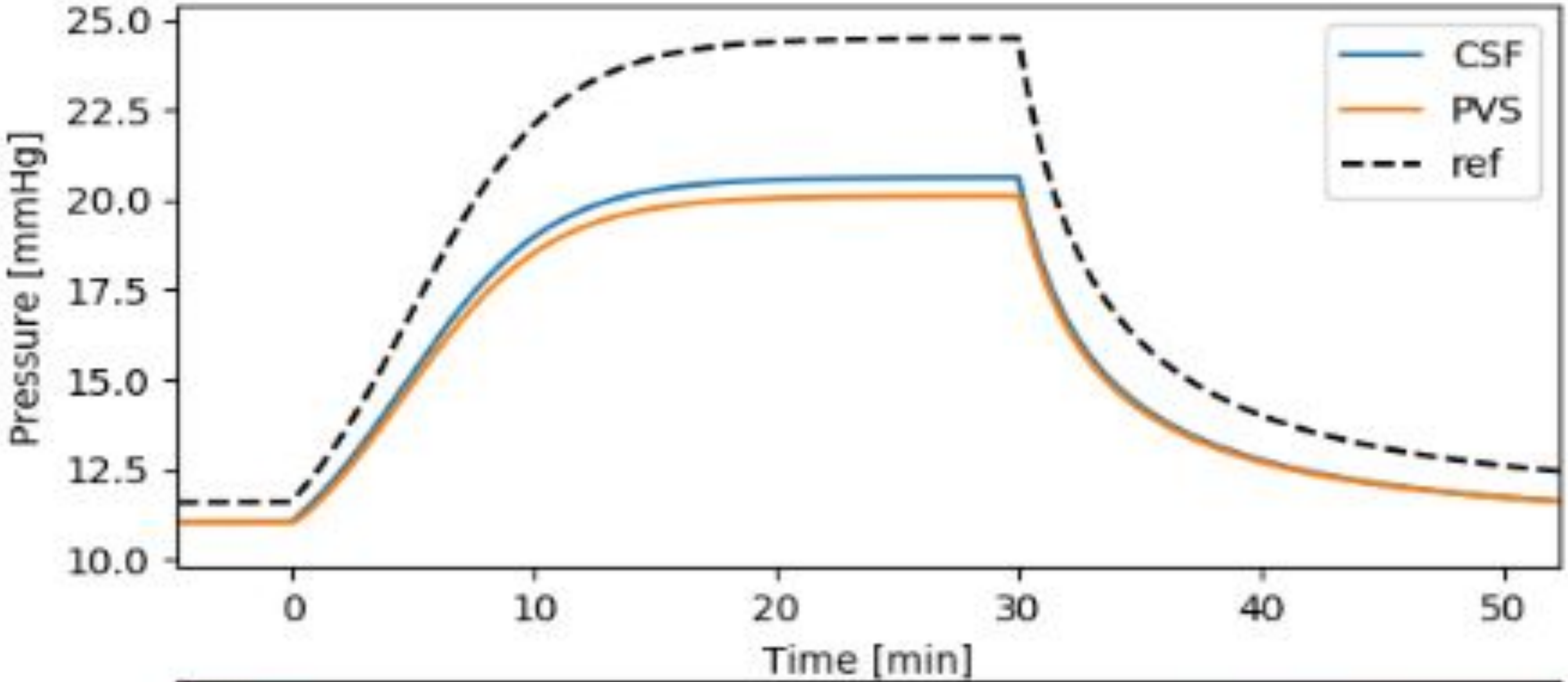


Arteries
Capillary bed
Veins
p_{cap}
R_{cap}
Paravascular space
Pial sleeves
p_{PVS}
R_{aPVS}
R_{gap}
R_{vPVS}
p_v
Extracellular space
Lymph space
R_{ECS}
$C_1(p_{PVS})$
Q_{inf}
p_{SAS}
Subarachnoid space
R_{crib}
p_{crib}
Dural sinus
Q_{prod}
R_{AG}
p_d
$C_0(p_{SAS})$
Compliance compartments

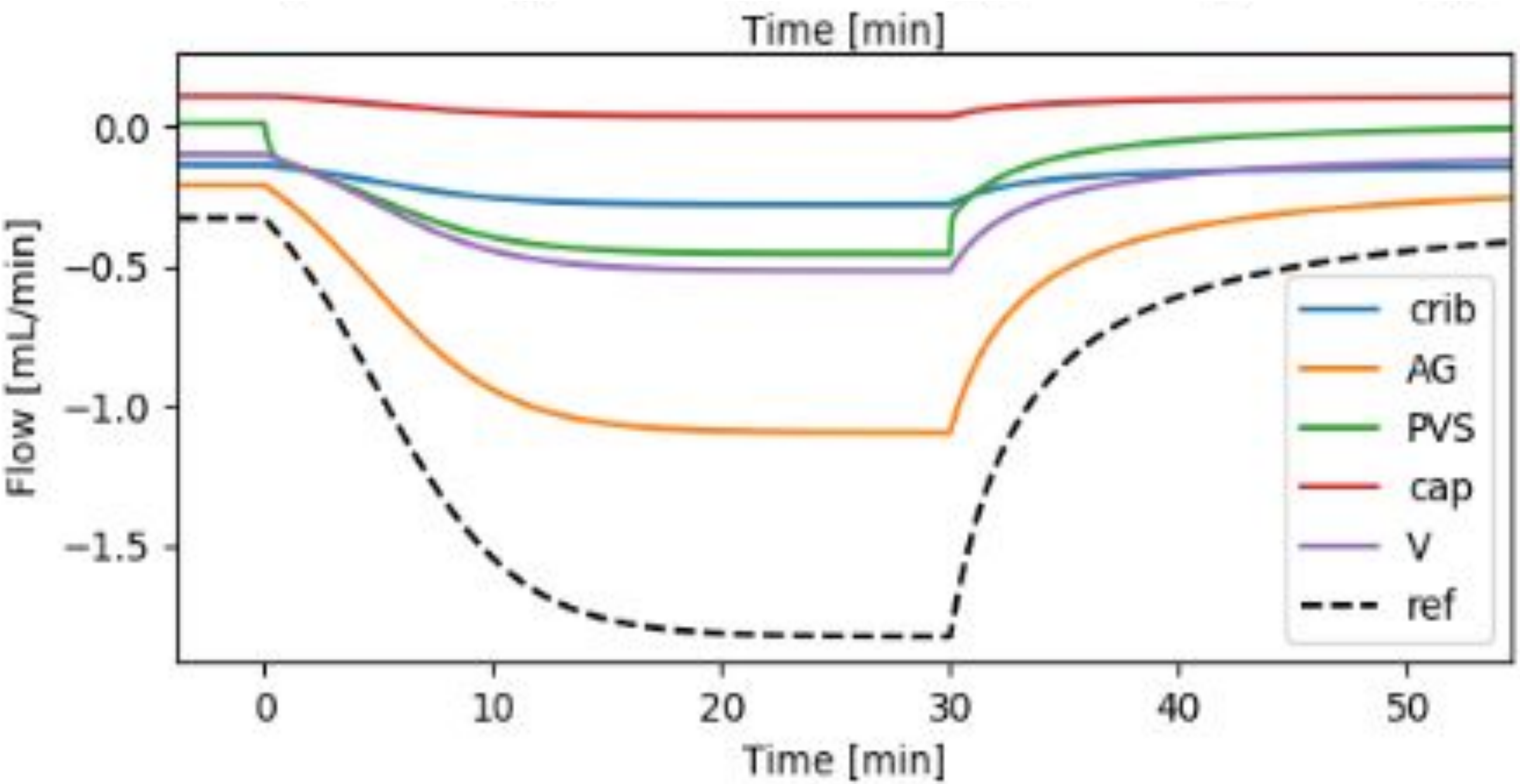


Arteries
Capillary bed
p_{cap}
25 mmHg
Veins
R_{cap}
Paravascular space
Pial sleeves
8.8 mmHg
p_{PVS}
R_{aPVS}
R_{gap}
R_{vPVS}
p_v
Extracellular space
Lymph space
R_{ECS}
$C_1(p_{PVS})$
2.0 mmHg
Q_{inf}
p_{SAS}
Subarachnoid space
R_{crib}
p_{crib}
Dural sinus
Q_{prod}
R_{AG}
p_d
8.8 mmHg
$C_0(p_{SAS})$
Compliance compartments

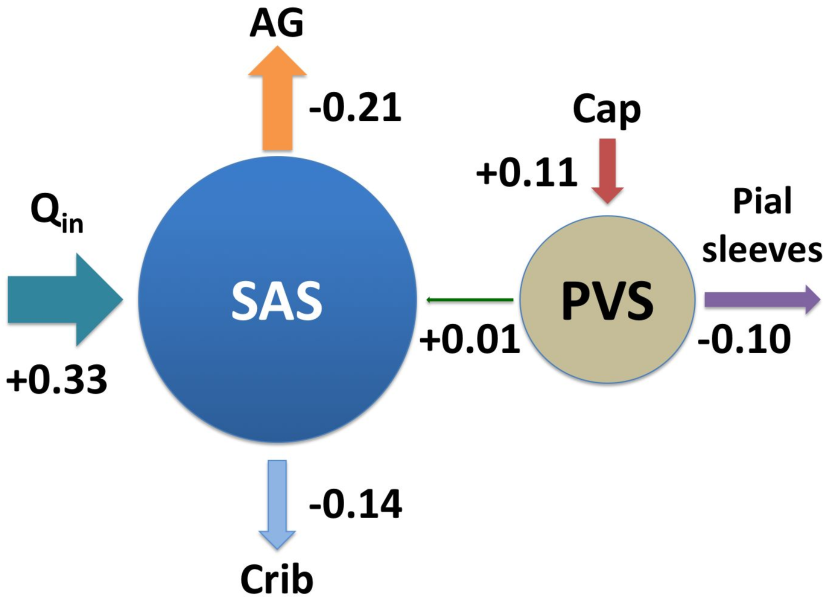
With the calculated resistances, R_{out} in our model were lower than median experimental values, but within variation for healthy patients



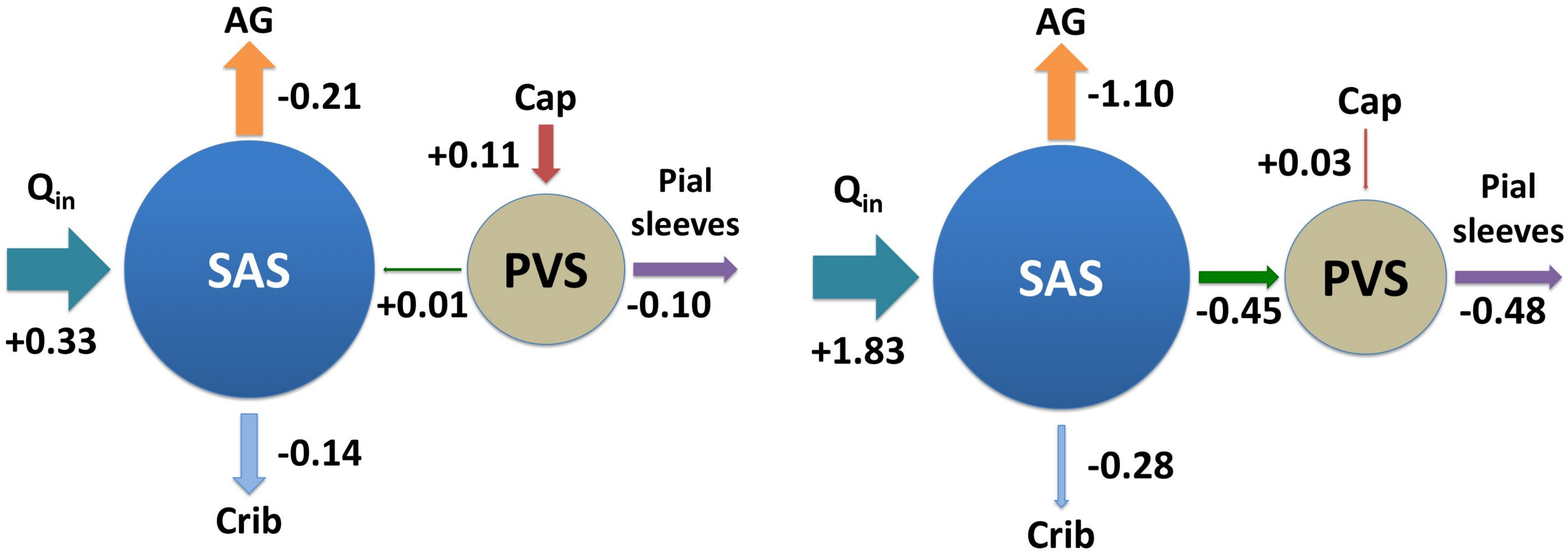
CSF outflow distribution is altered by infusion



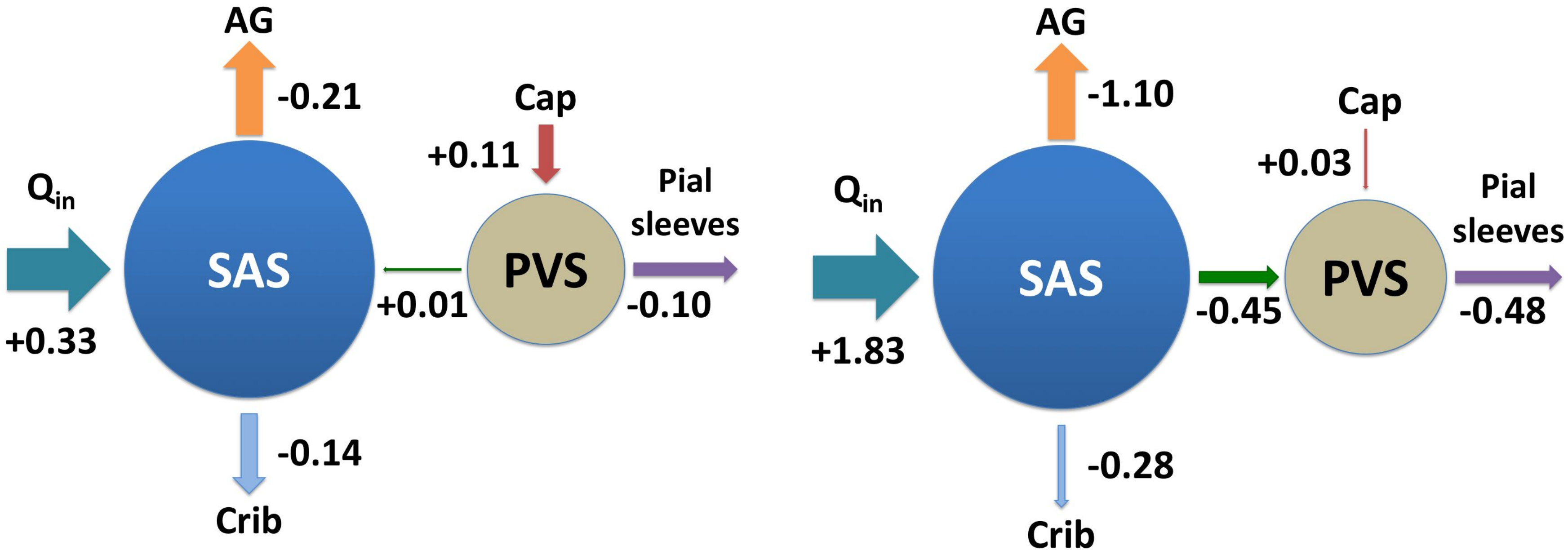
CSF outflow distribution is altered by infusion



CSF outflow distribution is altered by infusion



CSF outflow distribution is altered by infusion



Based on the volumetric flow rate, PVS velocities were calculated to be +0.04 and -2 μm/sec

We are currently investigating Starling forces related to capillary filtration

Other limitations include:

- Resistance parameters from several different species
- Lack of arterial and respiratory pulsations
- No spatial dependency
- Constant capillary pressure

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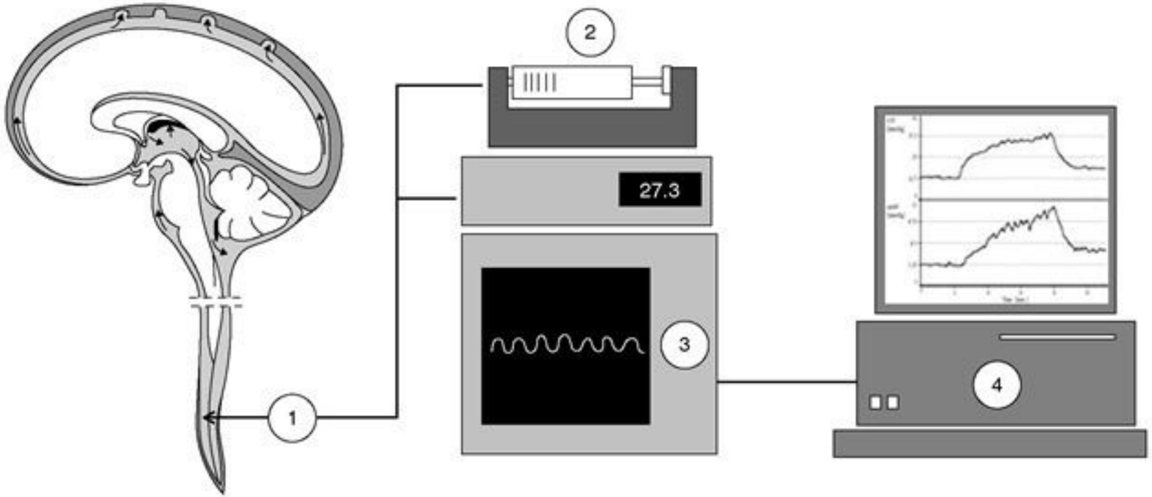

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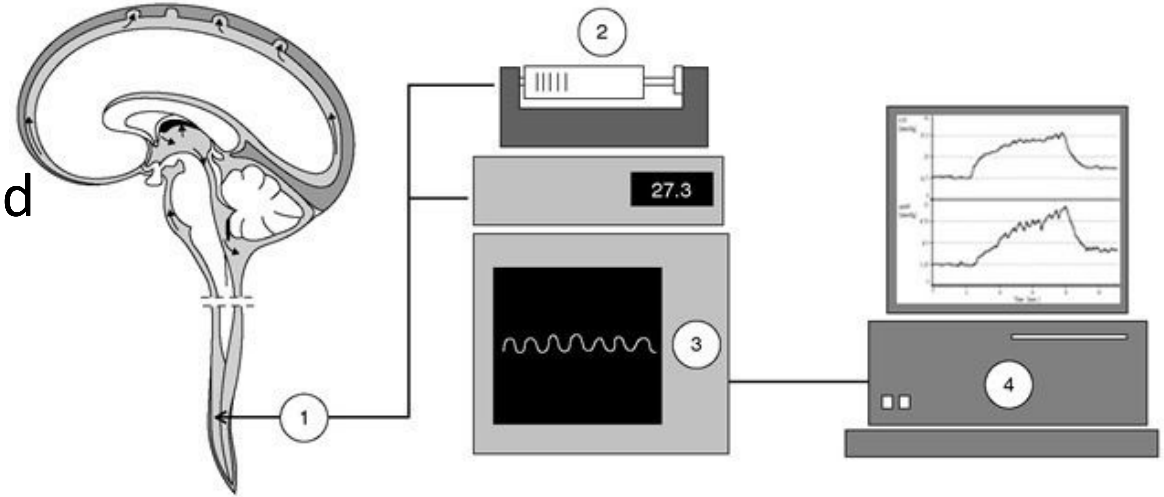
Thanks to:
Karen-Helene Støverud
Marie E. Rognes
Anders Eklund
Kent-Andre Mardal



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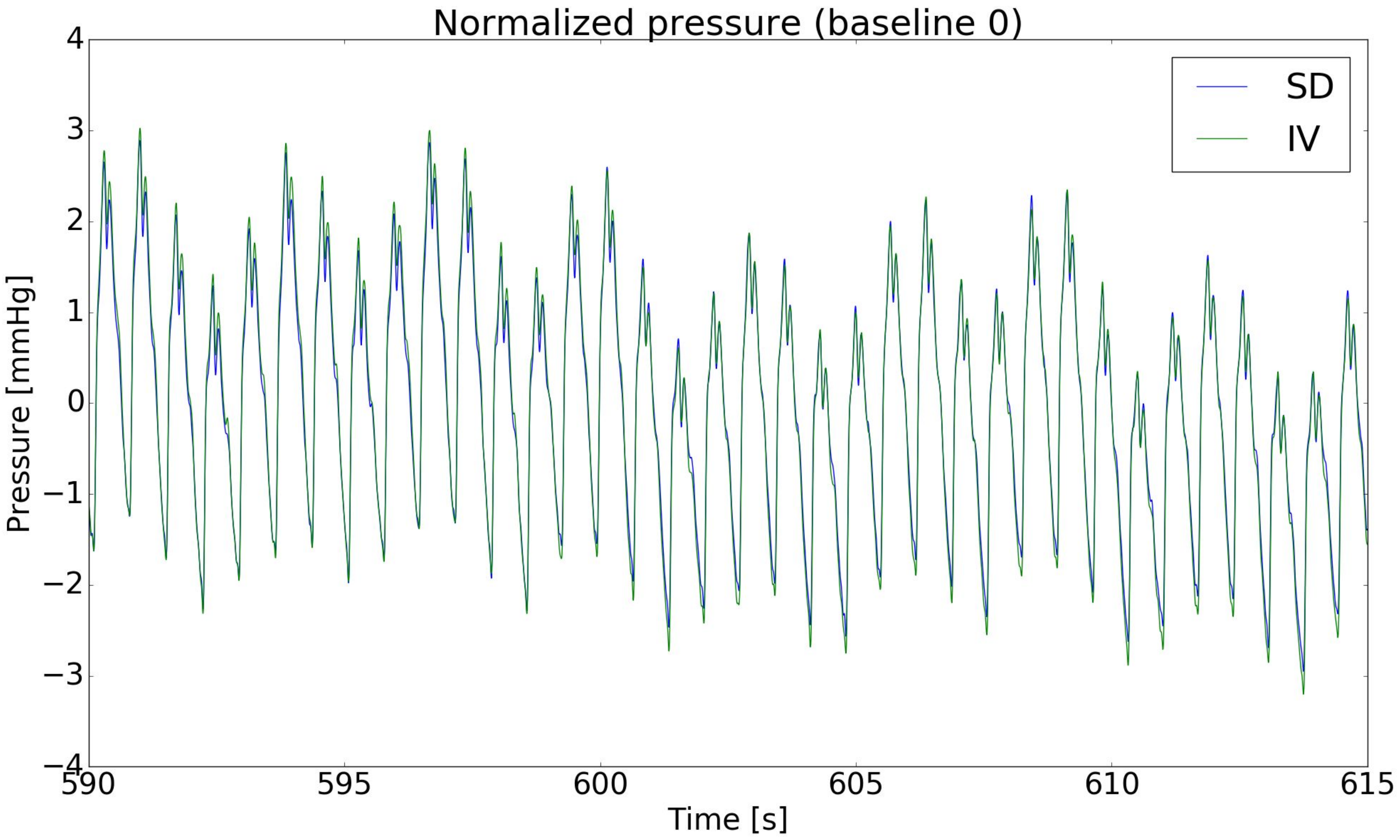
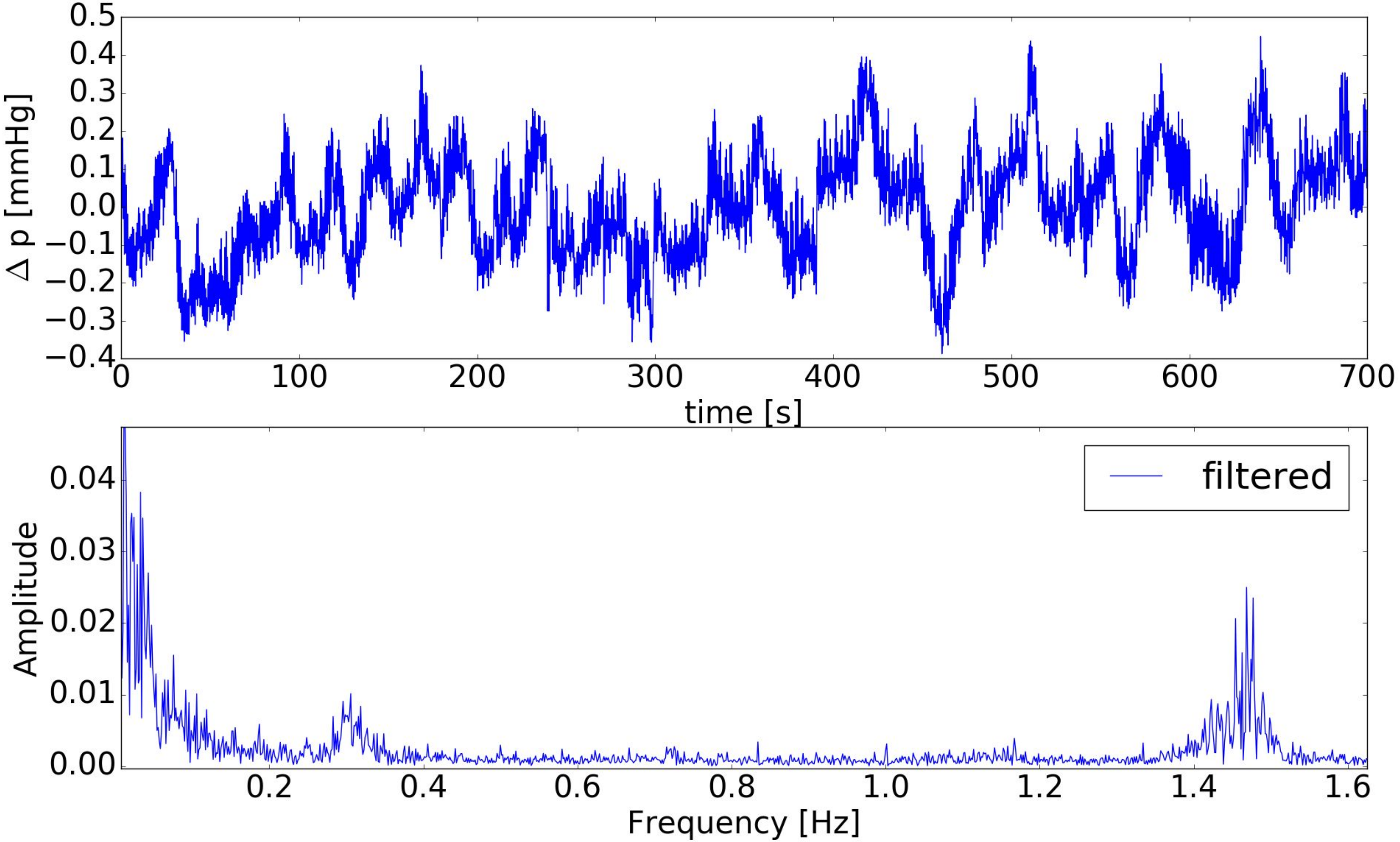
Model	R_{AG}	R_{crib}	R_{aPVS}	R_{cap}	R_V	p_V
0	8.6	∞	∞	∞	∞	8.8
1	10.81	67.0	1.14	125.31	22.96	8.8
2	10.81	∞	∞	∞	∞	8.8
3	10.81	67.0	∞	∞	∞	8.8
4	∞	67.0	1.14	125.31	22.96	8.8
5	21.62	67.0	1.14	125.31	22.96	8.8
6	10.81	67.0	1.43×10^{-3}	125.31	2.6×10^{-3}	8.8
7	10.81	67.0	1.14	125.31	22.96	2.0
8	10.81	67.0	1.14	125.31	22.96	$p_0(t)$
9	10.81	67.0	1.14	∞	22.96	8.8

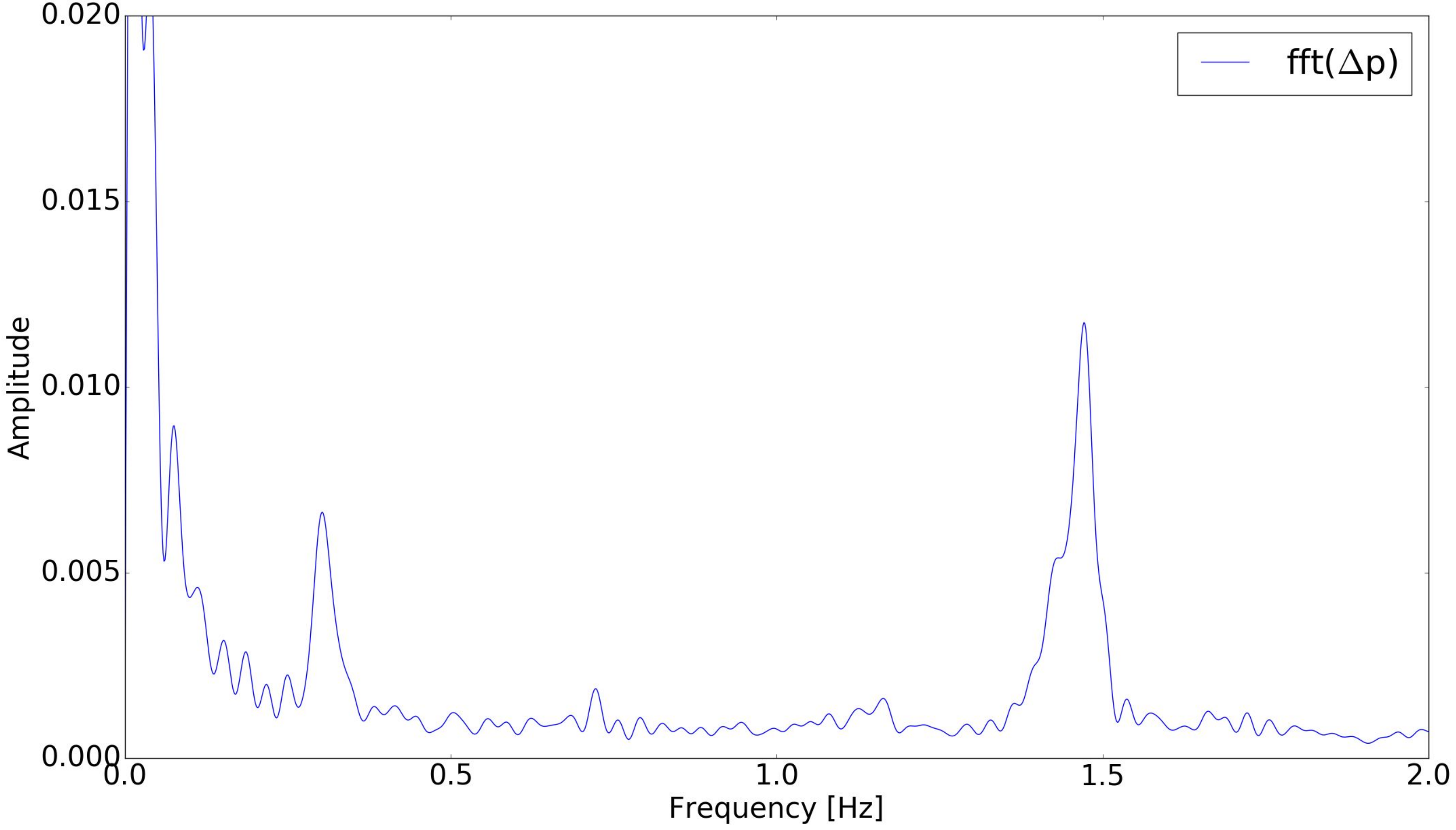
Mod	ICP (p_0)	AG flow	PVS flow	Crib flow	Cap flow	R_0	R_1
0	**11.66 (24.56)**	**-0.33 (-1.83)**	**n/a**	**n/a**	**n/a**	**8.60**	**n/a**
1	11.07 (20.68)	-0.21 (-1.10)	0.01 (-0.45)	-0.14 (-0.28)	0.11 (0.03)	6.41	6.05
2	12.39 (28.60)	-0.33 (-1.83)	n/a	n/a	n/a	10.81	n/a
3	10.95 (24.91)	-0.20 (-1.49)	n/a	-0.13 (-0.34)	0.11 (0.00)	9.31	n/a
4	14.34 (37.92)	n/a	-0.15 (-1.29)	-0.18 (-0.54)	0.09 (-0.10)	15.72	14.85
5	12.01 (25.67)	-0.15 (-0.78)	-0.03 (-0.70)	-0.15 (-0.35)	0.10 (-0.00)	9.10	8.60
6	8.82 (8.83)	-0.00 (-0.00)	-0.23 (-1.73)	-0.10 (-0.10)	0.13 (0.13)	0.00	0.00
7	9.27 (18.88)	-0.04 (-0.93)	-0.18 (-0.65)	-0.11 (-0.25)	0.13 (0.05)	6.41	6.05
8	11.92 (24.92)	-0.29 (-1.49)	0.10 (0.00)	-0.15 (-0.34)	0.10 (0.00)	8.66	8.66
9	10.35 (20.43)	-0.14 (-1.07)	-0.06 (-0.48)	-0.12 (-0.27)	n/a	6.71	6.40

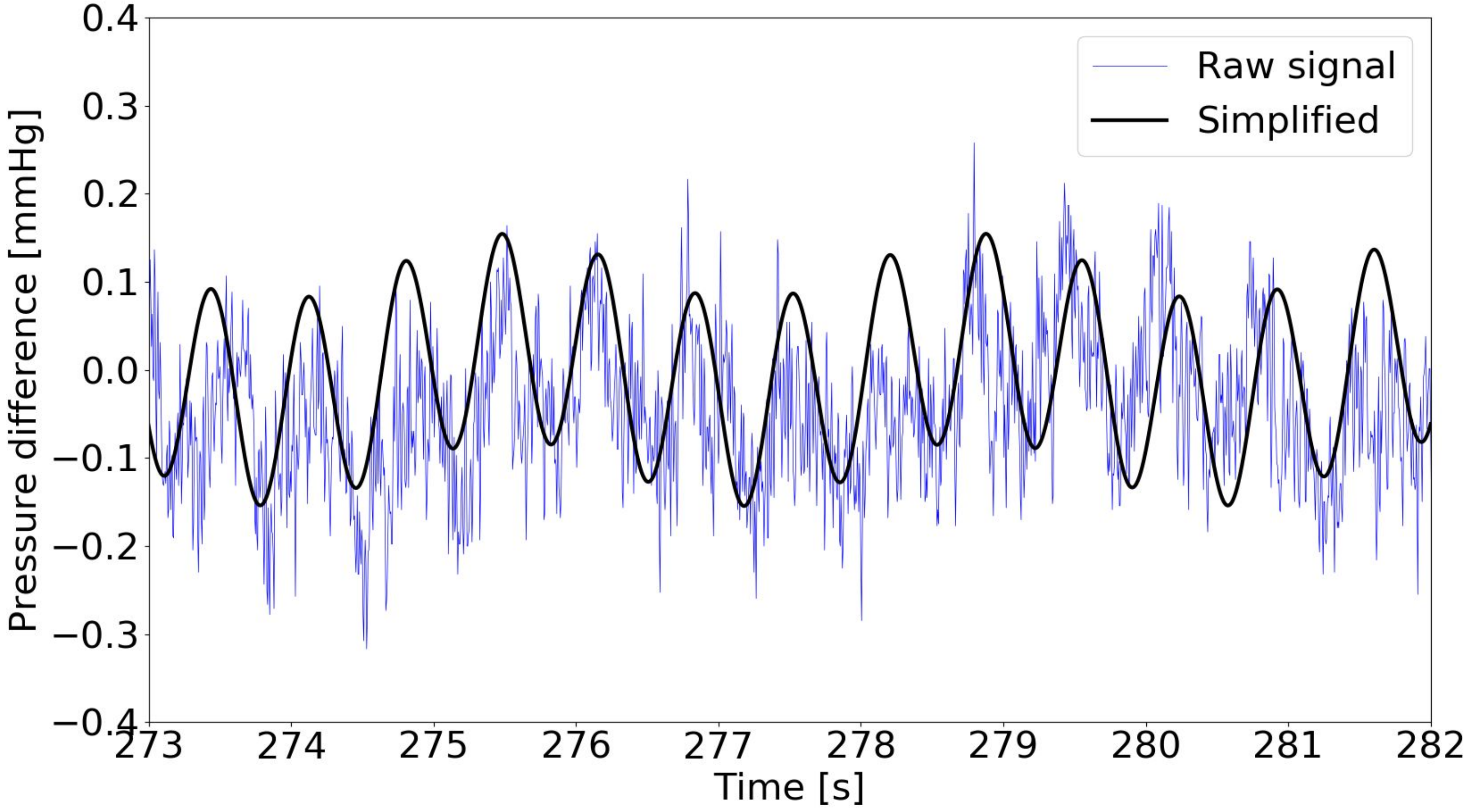


Normalized pressure (baseline 0)
SD
IV
Pressure [mmHg]
Time [s]
4
3
2
1
0
−1
−2
−3
−4
590
595
600
605
610
615



Δ p [mmHg]
0.5
0.4
0.3
0.2
0.1
0.0
−0.1
−0.2
−0.3
−0.4
0
100
200
300
400
500
600
700
time [s]
Amplitude
0.04
0.03
0.02
0.01
0.00
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
Frequency [Hz]
filtered


fft(Δp)
Amplitude
0.020
0.015
0.010
0.005
0.000
0.0
0.5
1.0
1.5
2.0
Frequency [Hz]



Raw signal
Simplified
Pressure difference [mmHg]
Time [s]
0.4
0.3
0.2
0.1
0.0
−0.1
−0.2
−0.3
−0.4
273
274
275
276
277
278
279
280
281
282