Persistent or relapsing symptoms post-treatment *PRESSURE*

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Conflicts and Funding

- None relevant to this topic
- MAB of Spinal CSF Leak Foundation
- MAB of Hydrocephalus Association
- Research grant supported by Fujirebio Diagnostics

- Generous funding provided by NIH and patients

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2014….

- 33 yr old woman, sudden orthostatic headaches following kayaking on the weekend
- MRI – classic dural enhancement, brainstem sagging, tonsillar descent
- CT myelo – T6 meningeal diverticulum
- Targeted blood patch failed
- Targeted fibrin patch succeeded

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But..

- Symptoms unchanged
- MRI normal
- Repeat CT myelo negative
- Only transient benefits with repeat empiric EBPs
- What next?

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No resolution

- ICP monitoring with orthostatic challenge
- Supine ICP: 5 to 10 mm Hg
- Upright ICP: -2 to 5 mm Hg
- Never developed papilledema, No venous stenosis or other risk factors for IIH
- Imaging burden: > 20 CTs, > 30 MRIs, > 10 CT Myelograms including DSM, dynamic CTM at reference centers, no early uptake of tracer in kidneys or bladder or radionuclide scans
- Cumulative radiation exposure?

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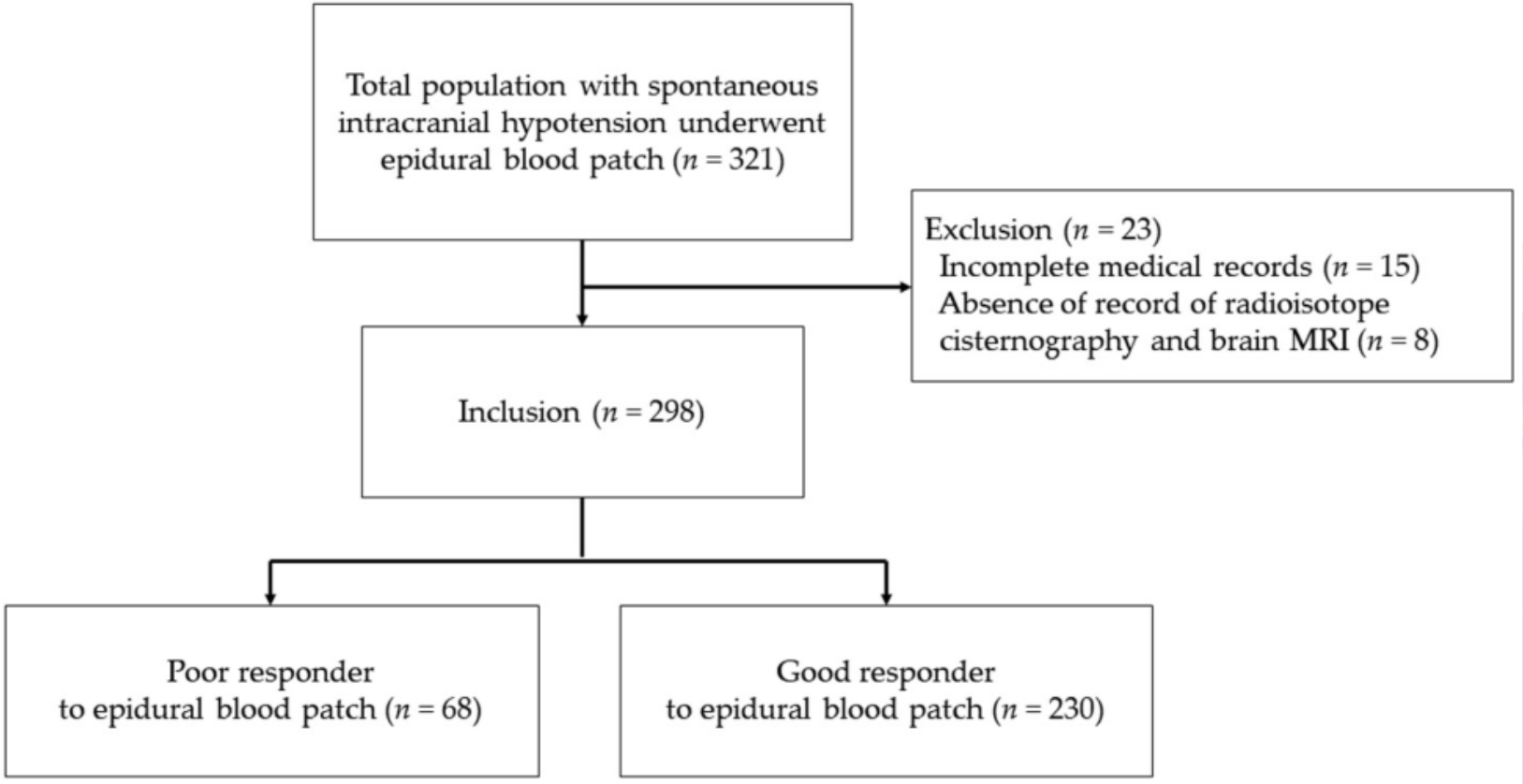
Poor responders to multiple EBPs 1:4



Park JY, Ro YJ, Leem JG, Shin JW, Oh Y, Choi SS. Predictors Associated with Outcomes of Epidural Blood Patch in Patients with Spontaneous Intracranial Hypotension. J Clin Med. 2021 Feb 28;10(5):922.

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Poor responders to multiple EBPs

No demographic or clinical factors predicted poor responders

Variables	Total Patients (n = 298)	Poor Responders (n = 68)	Good Responders (n = 230)	p-Value
Age, years	38 (33–46)	38 (34–46)	38 (33–46)	0.952
Sex				
Male/Female, n (%)	108 (36.2%)/190 (63.8%)	27 (39.7%)/41 (60.3%)	81 (35.2%)/149 (64.8%)	0.499
Height, cm	164.6 ± 22.3	165.4 ± 8.9	164.4 ± 8.2	0.365
Weight, kg	58.0 (52.3–68.0)	58.5 (52.1–69.0)	58.0 (52.4–67.9)	0.816
Body mass index, kg/m^2	22.3 ± 2.9	21.9 ± 2.8	22.4 ± 2.9	0.270
Underlying disease				
Diabetes mellitus, n (%)	12 (4.0%)	1 (1.5%)	11 (4.8%)	0.310
Hypertension, n (%)	15 (5.0%)	0 (0.0%)	15 (6.5%)	0.027
Coronary arterial disease, n (%)	6 (2.0%)	3 (4.4%)	3 (10.3%)	0.130
Cerebrovascular accident, n (%)	1 (0.3%)	0 (0.0%)	1 (0.4%)	>0.999
Herniated intervertebral disc, n (%)	10 (3.4%)	2 (2.9%)	8 (3.5%)	>0.999
History of headache				
Migraine, n (%)	11 (3.7%)	5 (7.4%)	6 (2.6%)	
Tension headach, n (%)	3 (1.0%)	0 (0.0%)	3 (1.3%)	0.613
Cluster headache, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Associated symptoms				
Nausea, n (%)	166 (55.7%)	42 (61.8%)	124 (53.9%)	0.194
Vomiting, n (%)	100 (33.6%)	29 (42.6%)	71 (30.9%)	0.056
Photophobia, n (%)	2 (0.7%)	1 (1.5%)	1 (0.4%)	0.400
Hearing impairment, n (%)	4 (1.3%)	2 (2.9%)	2 (0.9%)	0.220
Tinnitus, n (%)	65 (21.8%)	8 (11.8%)	24 (10.4%)	0.723
Vertigo, n (%)	1 (0.3%)	0 (0.0%)	1 (0.4%)	>0.999
Diplopia, n (%)	1 (0.3%)	0 (0.0%)	1 (0.4%)	>0.999
Duration of headache, days	10.0 (9.0–30.0)	15.0 (9.0–30.0)	10.0 (9.0–30.0)	0.579
Headache, numeric rating scale	7.0 (5.0–9.0)	7.0 (4.0–9.0)	7.0 (5.0–8.0)	0.790

Data are expressed as the mean ± standard deviation, median (interquartile range), or number (%). Poor responders, patients who underwent epidural blood patch three or more times; good responders, patients who underwent epidural blood patch one or two times.

Poor responders to multiple EBPs

No differences in imaging characteristics

Variables	Total Patients (n = 298)	Poor Responders (n = 68)	Good Responders (n = 230)	p-Valu
Brain MRI signs				
Pachymeningeal enhancement, n (%)	161 (54.0%)	35 (51.5%)	126 (54.8%)	0.542
Engorgement of venous structures, n (%)	101 (33.9%)	29 (42.6%)	72 (31.3%)	0.095
Brain sagging, n (%)	40 (13.4%)	7 (10.3%)	33 (14.3%)	0.367
Pituitary hyperemia, n (%)	32 (10.7%)	7 (10.3%)	25 (10.9%)	0.864
Midline shift, n (%)	5 (1.7%)	0 (0.0%)	5 (2.2%)	0.592
Midbrain–pons angle, degrees	55.3 ± 10.0	55.0 ± 8.8	55.3 ± 10.4	0.800
Vein of Galen–Straight sinus angle, degrees	63.4 (46.6–74.1)	64.1 (43.0–74.6)	63.1 (47.5–73.5)	0.934
Cisternography				
Level of cerebrospinal fluid leakage				
Cervical, n (%)	132 (44.3%)	29 (42.6%)	103 (44.8%)	0.755
Thoracic, n (%)	153 (51.3%)	37 (54.4%)	116 (50.4%)	0.564
Lumbar, n (%)	64 (21.5%)	19 (27.9%)	45 (19.6%)	0.140
Undetermined, n (%)	45 (15.1%)	6 (8.8%)	39 (17.0%)	0.100
Multiple leakage, n (%)	160 (53.7%)	43 (63.2%)	117 (50.9%)	0.159
Cerebrospinal opening pressure, mmHg	4.8 (0.0–8.0)	4.5 (0.0–7.5)	5.0 (0.0–8.2)	0.580
Early bladder activity, n (%)	59 (19.8%)	17 (25.0%)	42 (18.3%)	0.369

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ICP Monitoring for SIH

- ICP Monitoring 2015 – current: 291
- ICP Monitoring for SIH: 74
- F:M – 2:1
- Mean Age: 34 ± 8 yrs
- Overnight ICP monitoring supine followed by Orthostatic challenge – inclined 45^{o}, sitting, standing

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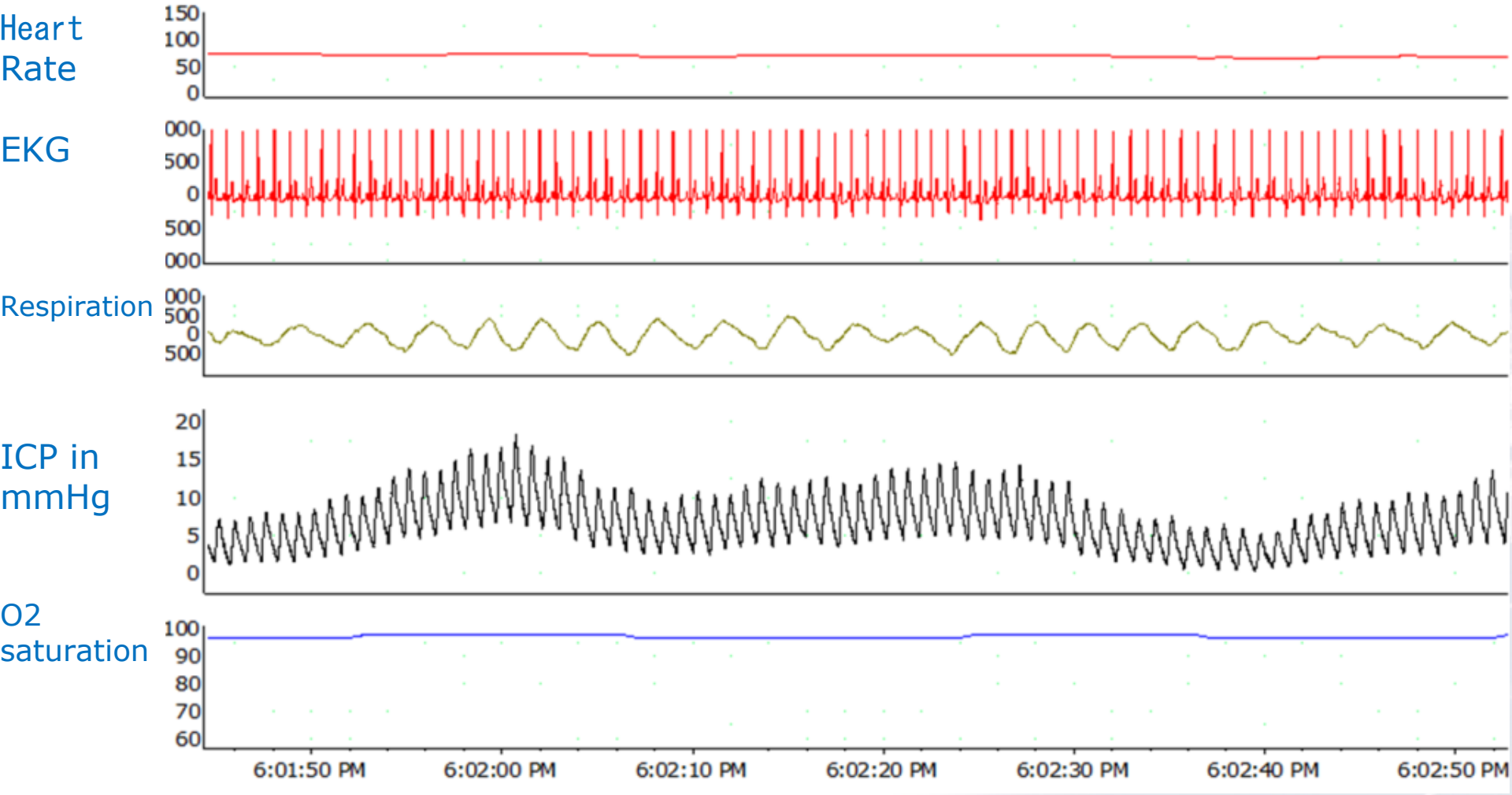
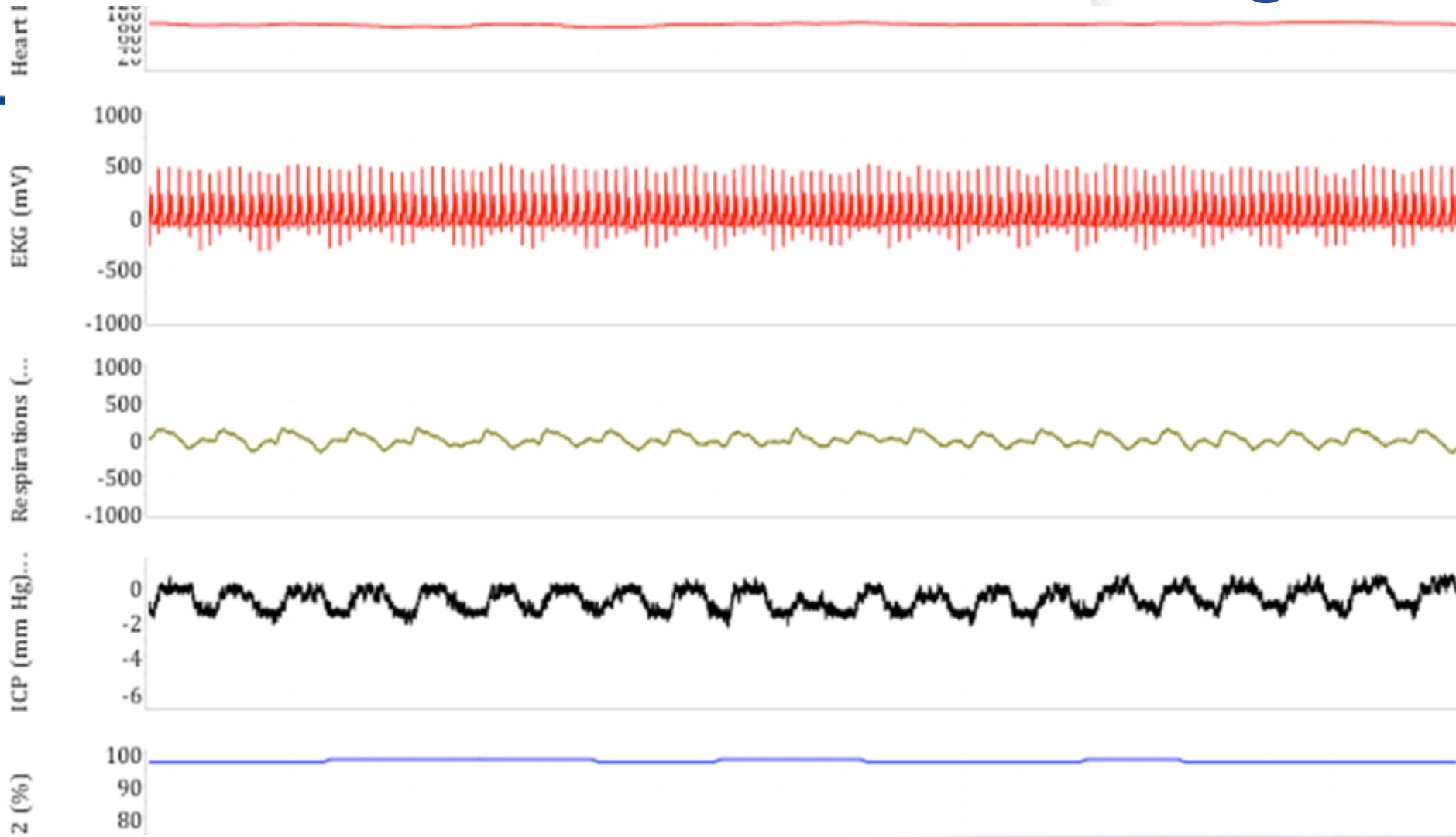
Physiologic ICP – cardiac and respiratory modulation



No CSF Leak – ICP while sitting



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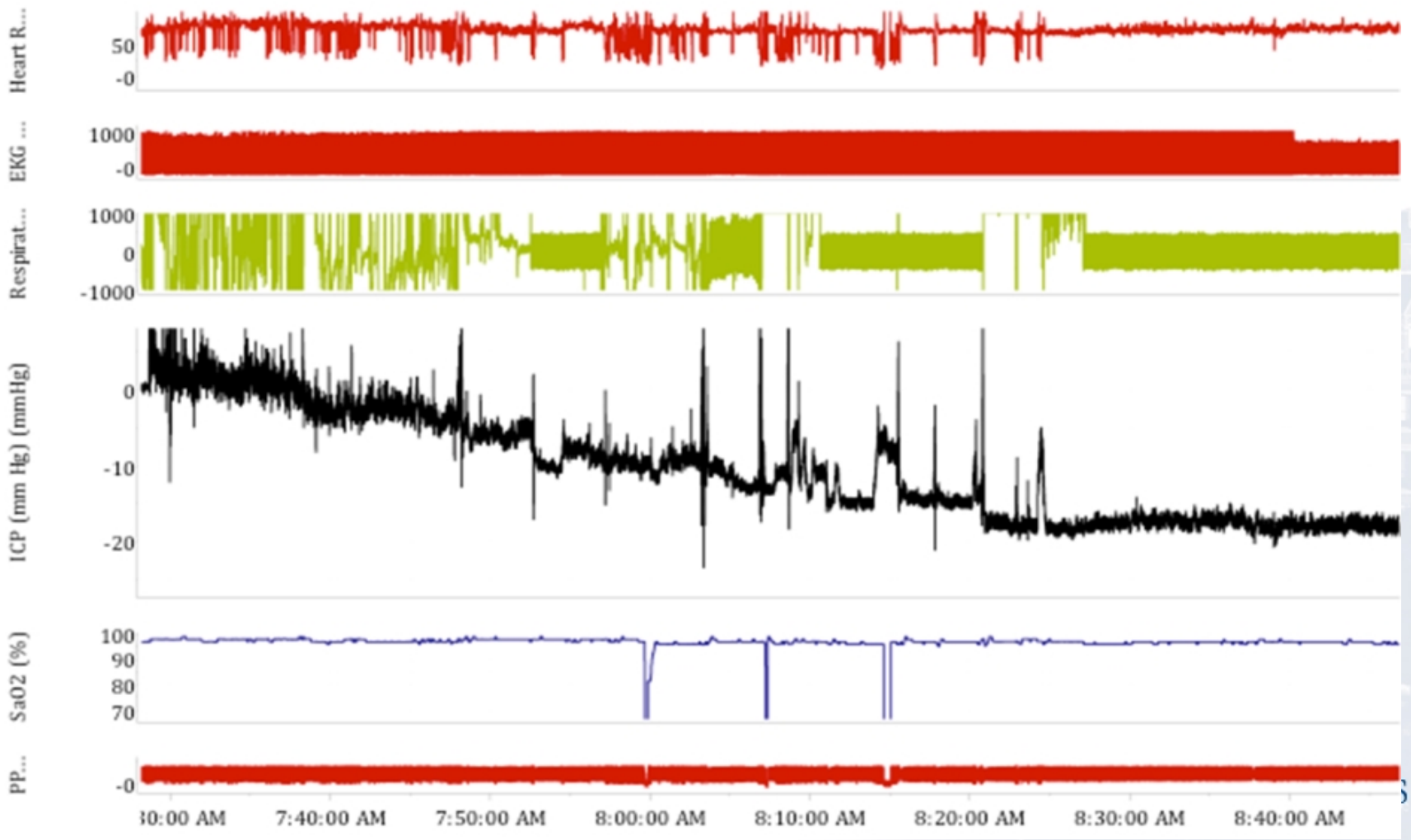
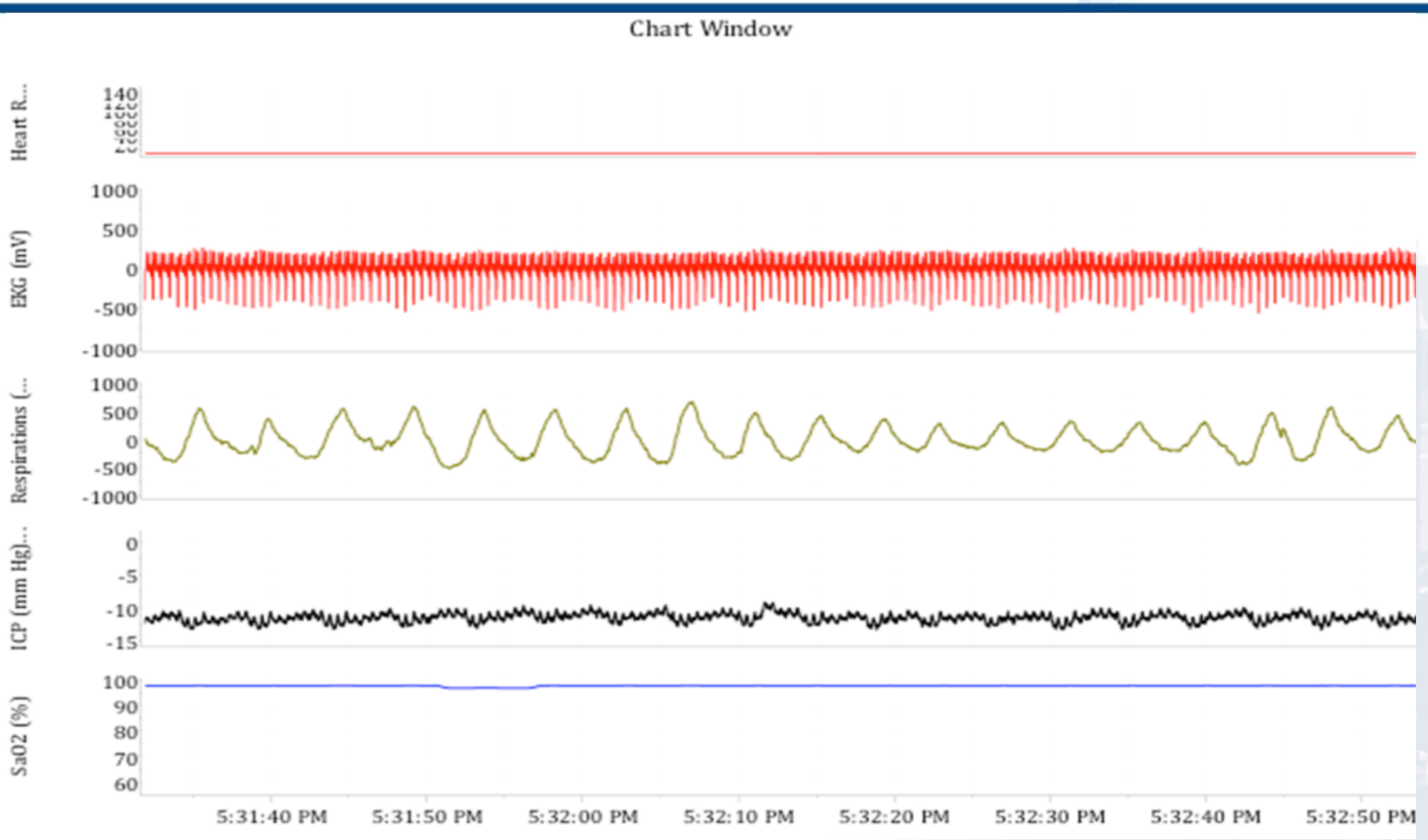
Spinal CSF Leak – Bolt Patch protocol



SIH – multiple perineural diverticula



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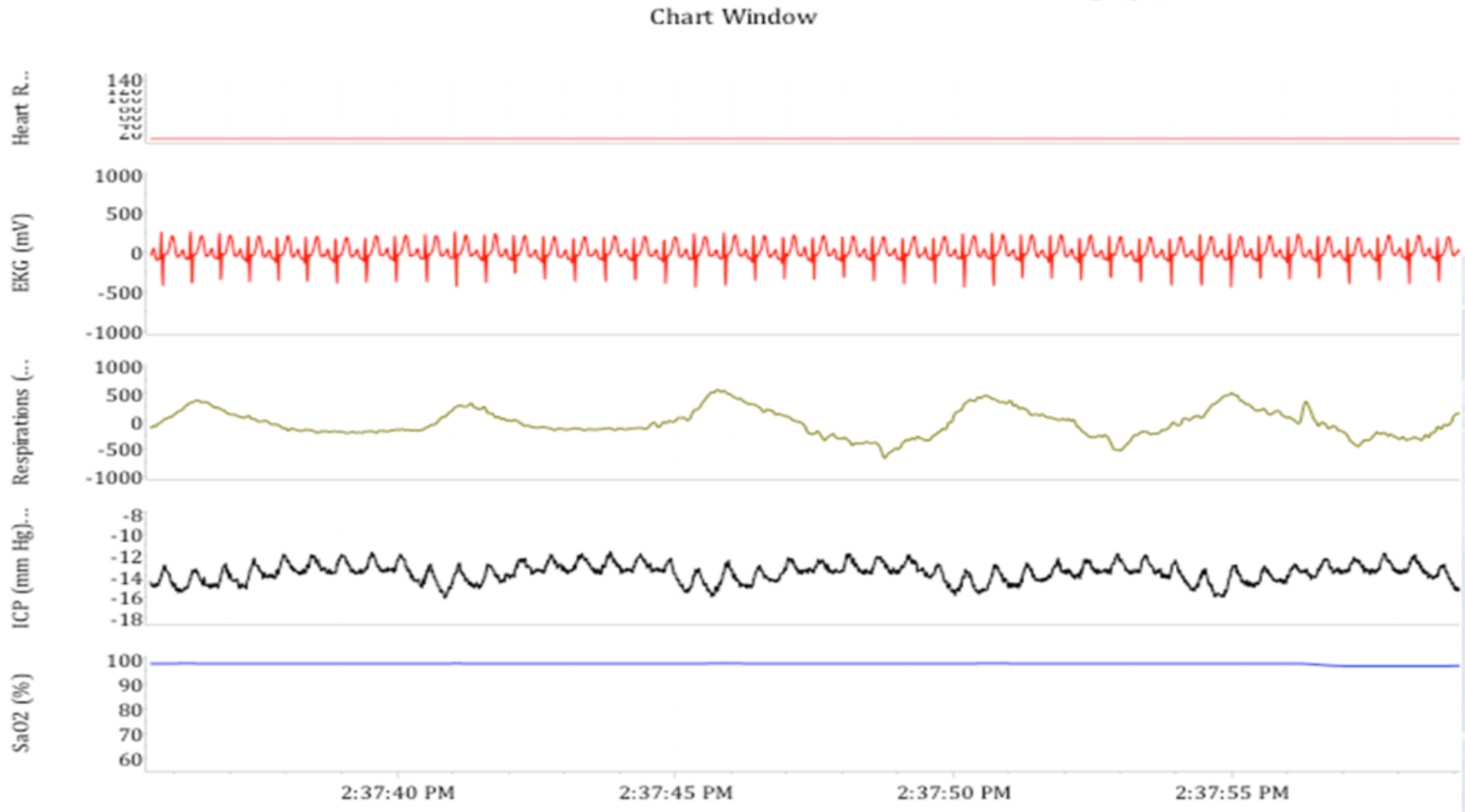
SIH – CSF venous fistula



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Outcomes

- Orthostatic ICP < -10 mmHg: 4 / 74

- What about the rest ?

  Chronic migraines
  Tension type headaches
  New daily persistent headaches
  POTS

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Treatments

- Topamax
- SNRIs/SSRIs
- Botox
- TCAs
- CGRP antagonists
- Calcium channel blockers

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More than just a headache……

- Fatigue
- Mental fog
- Dizziness
- Malaise
- Hearing loss, tinnitus
- Memory impairment
- Insomnia

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Multiple Mechanisms

- Sympathetic and parasympathetic dysfunction
- Inflammatory milleu
- Mechanical Sensitization

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Mechanism of nociception in low pressure headaches

- No baroreceptors in brain or meninges unlike carotid bodies
- What mediates the pain in low pressure syndromes

Role of ***Piezo*** – mechanosensitive ion channels

Activated by stretching, pulling, pushing, exposure to hypo- or hyper-osmotic solutions, and flow-induced shear stress

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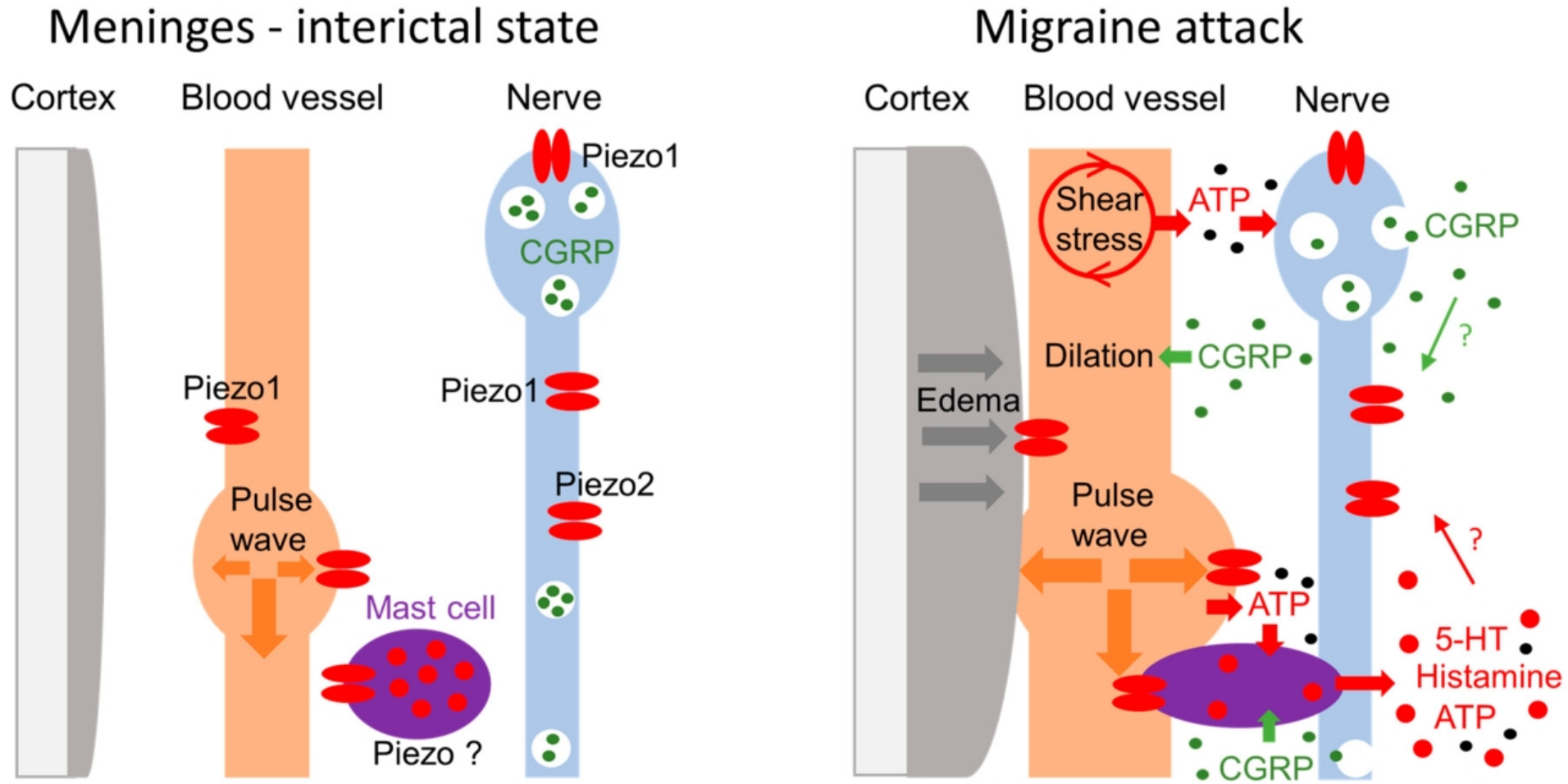
Stretch induced nocciception



Della Pietra, A.; Mikhailov, N.; Giniatullin, R. The Emerging Role of Mechanosensitive Piezo Channels in Migraine Pain. *Int. J. Mol. Sci.* **2020**, *21*, 696.

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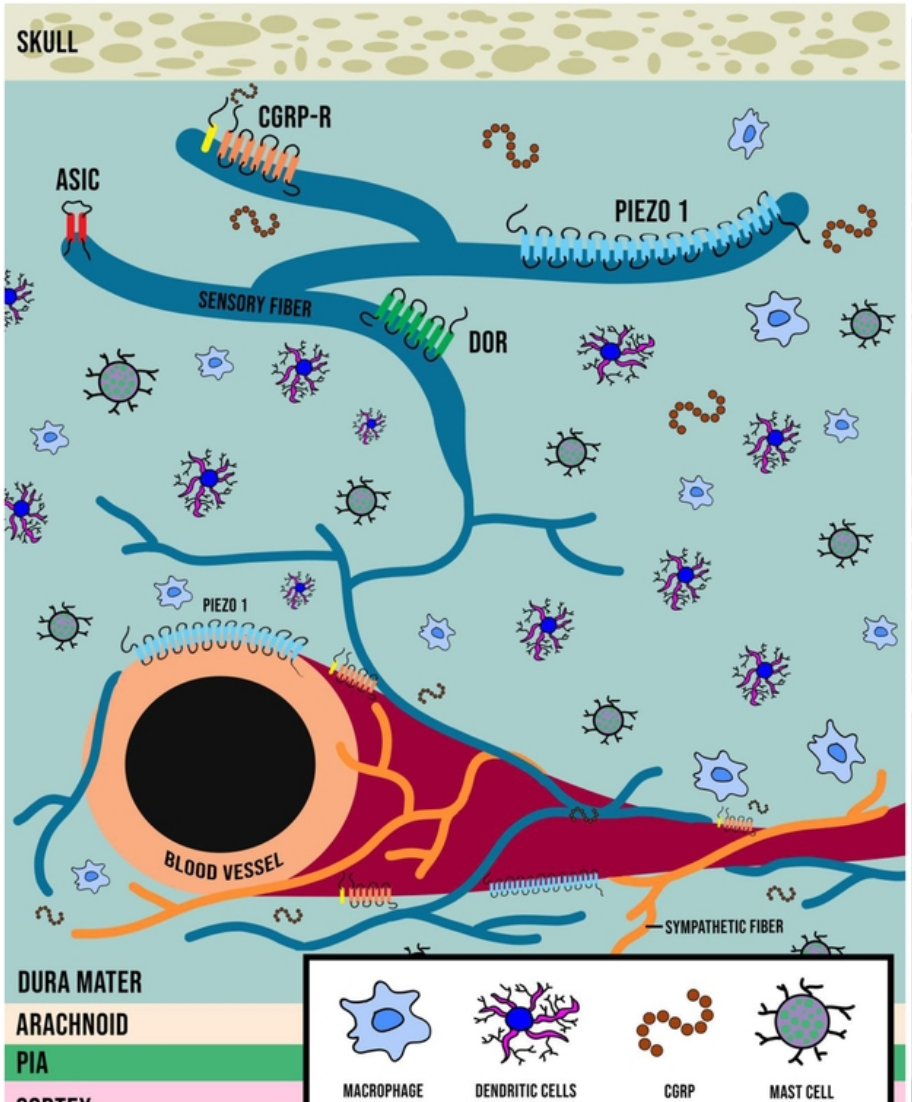
Evolving (lack of) understanding of nocciception



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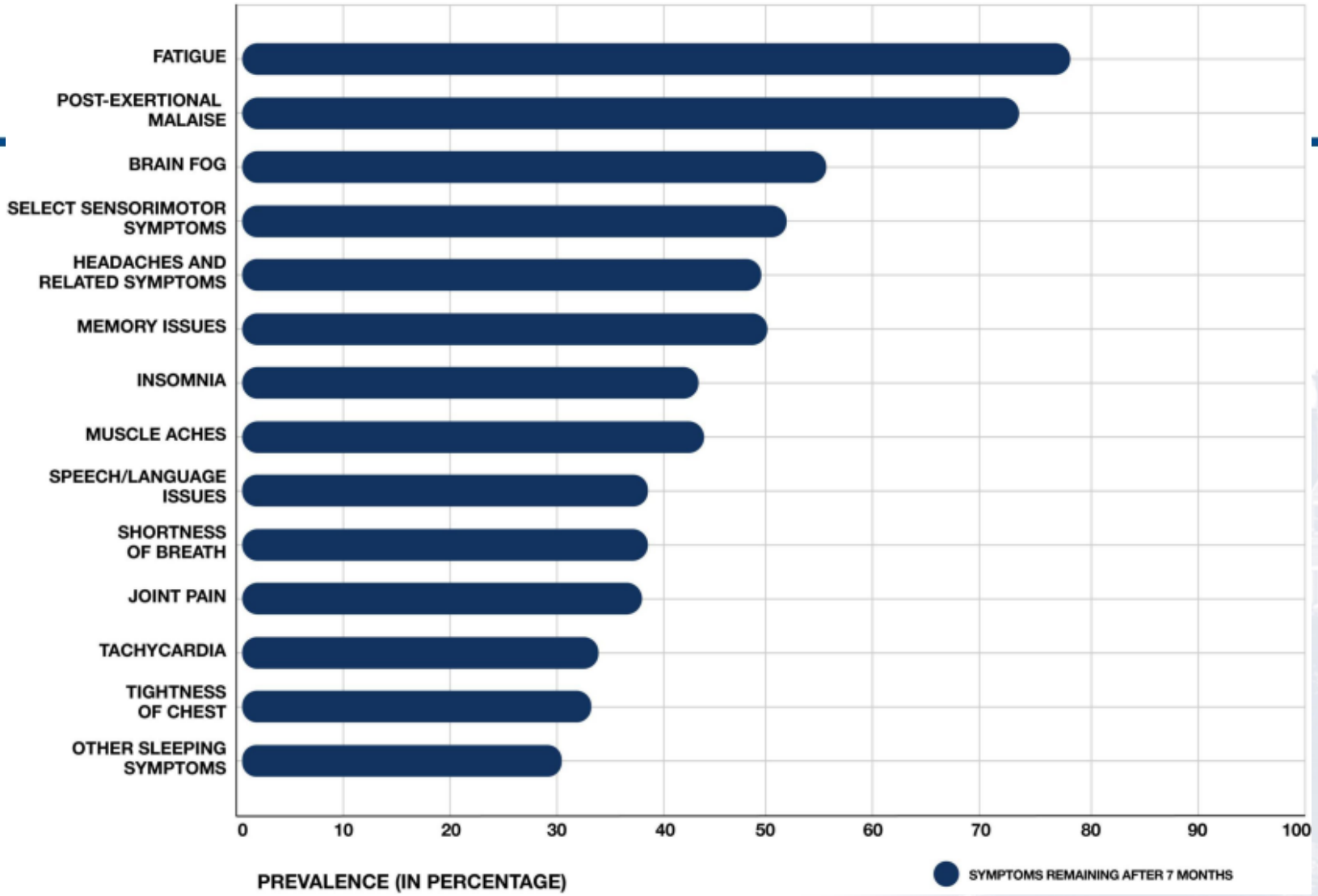

Proal AD, VanElzakker MB. Long COVID or Post-acute Sequelae of COVID-19 (PASC): An Overview of Biological Factors That May Contribute to Persistent Symptoms. Front Microbiol. 2021 Jun 23;12:698169.

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PASC – Post Acute Sequelae of Covid19

- Analogous to Myalgic Encephalitis
- Post-Viral Syndrome following EBV infection

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What is common to all such disorders?

- Heterogeneous
  - Persistent symptoms or evolution
  - New-onset symptoms
- Spectrum of physical, social and psychological consequences
- Different pathophysiologic processes

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PRESSURE-CSF

Persistent, Relapsing or Extended SIH
Symptoms despite Undetectable
Radiologic Evidence of CSF leak

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Proposed Study – 1
Natural History

- Multi-site
- Prospective
- Strict inclusion/exclusion criteria –
  - DSM in lateral decubitus position negative
  - MRI Brain with contrast negative
  - Bern Score ≤ 2
  - For those with persistent epidural or paraspinal fluid collections, ICP monitoring with orthostatic ICP > -10 mm Hg or normal CSF outflow resistance 5-10 mmHg/ml/min
  - Tilt-table negative
  - Exclude underlying IIH – LP, neuroopthalmology

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Proposed Study - 1

- Outcomes:
  - Clinical characteristics that predispose to higher risk
  - Cognitive: neuropsychological assessment
  - Affective: GAD-7, PHQ-9, IESR
  - Imaging – Volumetrics, CBVR, DTI, rsMRI
  - Biomarkers – CRP, IL6, Ferritin, Cortisol
  - Functional Status

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Proposed Study 2

- Test of the hypothesis that a “pressure reset” occurs in some
- Are repeated empiric EBPs effective?
- Only treatment that works despite negative imaging studies

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Proposed Study 2

- Randomized blinded sham trial – blood vs normal saline

- Scavone BM, Wong CA, Sullivan JT, Yaghmour E, Sherwani SS, McCarthy RJ. Efficacy of a prophylactic epidural blood patch in preventing post dural puncture headache in parturients after inadvertent dural puncture. Anesthesiology. 2004 Dec;101(6):1422-7

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Proposed Study 3

- Multimodal intervention vs routine care
- Multimodal:
  - Prophylactic Medication
  - Graduated exercise
  - TM/Yoga/Mindfulness
  - Vagal nerve stimulation

Eg: FINGER study

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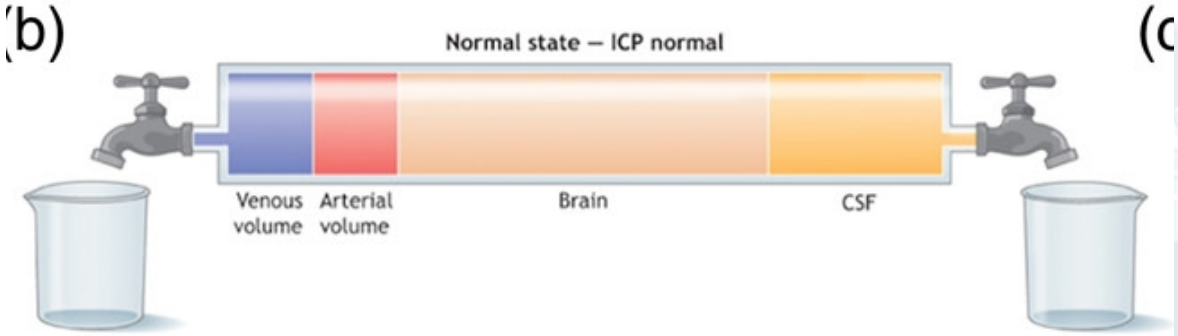
Low Pressure vs Low Volume



- In a fixed volume (skull) lowering volume of its non-distensible contents (CSF) should lower pressures

OR

- If cerebral blood volume compensates for the low CSF volume, the venous distention (compliant vessels) should be seen on contrast enhanced MRI

Wilson MH. Monro-Kellie 2.0: The dynamic vascular and venous pathophysiological components of intracranial pressure. J Cereb Blood Flow Metab. 2016 Aug;36(8):1338-50.

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Slippery Slope – higher bar for evidence

- You cannot have a syndrome of SIH with both Normal orthostatic ICP and Normal MRI
  - IIH without papilledema with normal ICP
  - Idiopathic NPH – The Emperor has no clothes

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Thanks

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