

The Link Between Poor Sleep and Impaired Clearance of Toxins is Breathing

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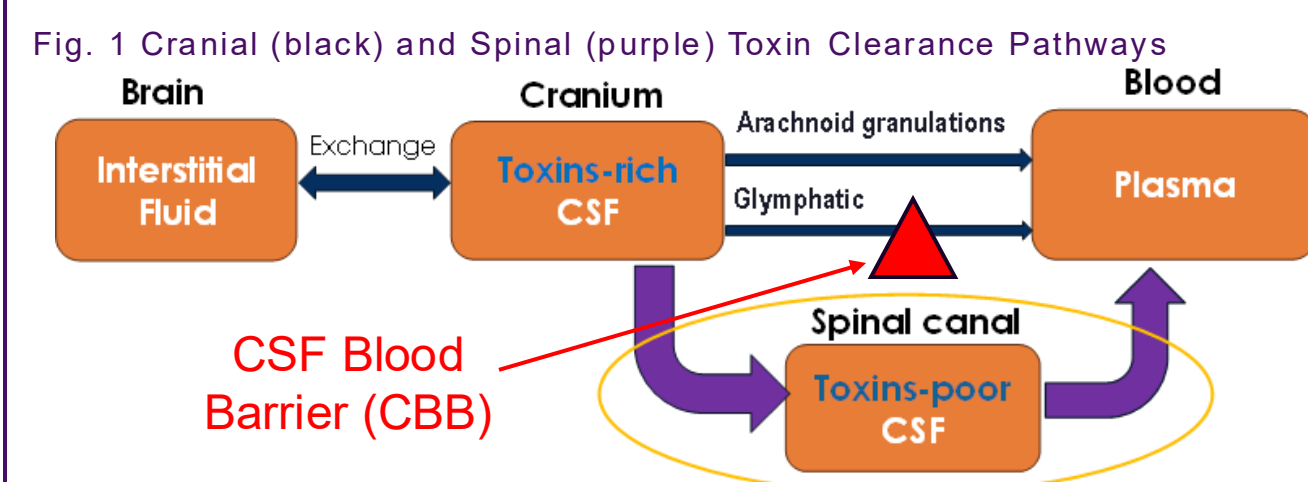
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The utilization of the spinal toxin clearance route is regulated by thoracic pressure which changes during different sleep stages.

The transfer of cranial soluble toxins to the spinal CSF occurs via the cranio-spinal CSF oscillation where a volume of CSF is displaced between the cranium and the spinal canal during each respiration cycle. The amplitude of the csCSF oscillation is inversely proportional to the amplitude of the thoracic expansion.

INTRODUCTION

- Elevated toxin load and accelerated tissue loss in AD-critical brain regions are evident in elderly poor sleepers, suggesting impaired clearance due to poor sleep.^{1,2}
- Current research focuses on cranial pathways: arachnoid granulations, glymphatics, and meningeal lymphatic vessels. None have shown sleep dependency^{3,4} (Fig. 1).



- We propose a **sleep dependent spinal route** where toxin-rich cranial CSF is displaced to the spinal canal via cranial-spinal (cs)CSF oscillation and cleared through spinal absorption sites.^{5,6}

- The displaced csCSF volume is controlled by breathing related changes in thoracic pressure. Since the csCSF flow is driven by the difference between arterial inflow and venous outflow, changes in venous outflow impact the csCSF flow.^{5,7}
- Changes in the right atrial pressure influence venous outflow.

METHODS

Measurement of the displaced csCSF volume

- To quantify the impact of breathing on the oscillating displaced csCSF volume, blood and csCSF flow were imaged during normal breathing (NB) and during slow deep breathing, simulating flow during deep sleep.
- Real-time phase-contrast MRI (Vida 3T Siemens) was employed to measure arterial inflow (A), venous outflow (V), and csCSF flow at the upper cervical spine in 8 healthy volunteers (Fig. 3).

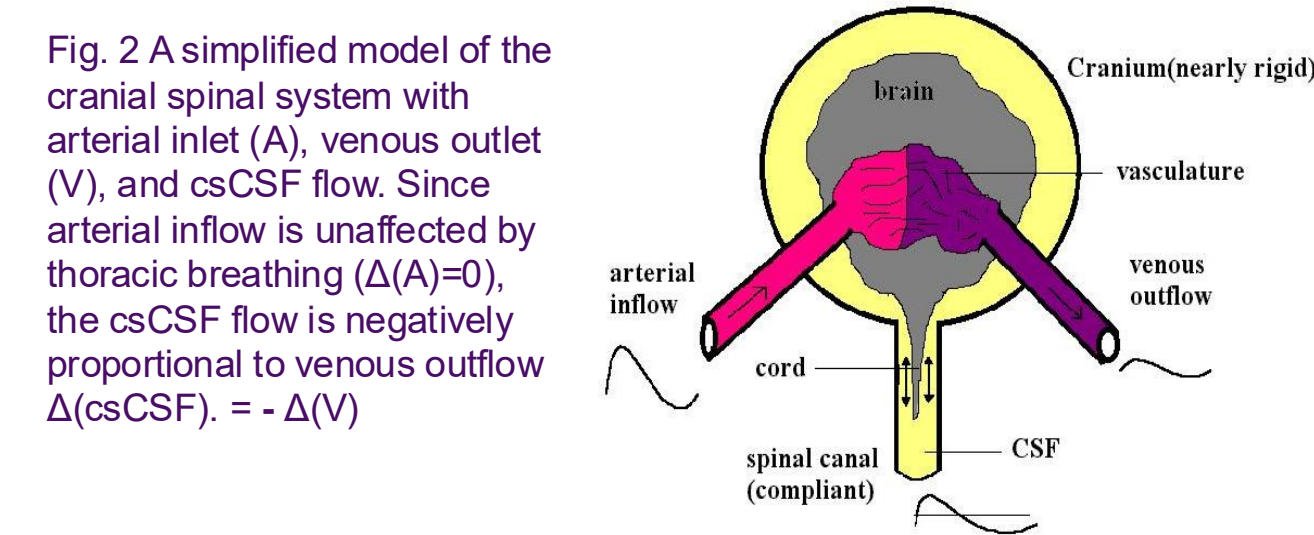
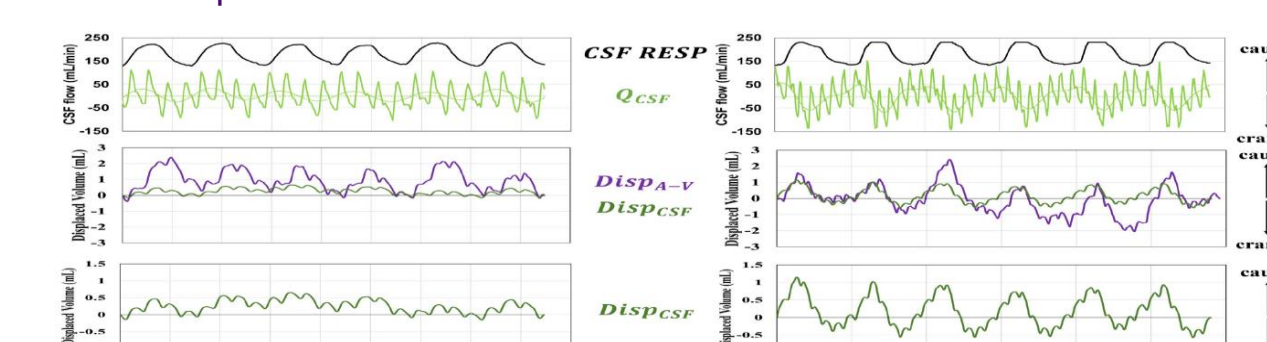


Fig. 3 Respiration and csCSF flow (upper trace), displaced arterial inflow – venous outflow (middle trace), and displaced csCSF flow (lower trace). Maximal displaced csCSF volume during simulated deep sleep (right) is significantly higher (57%) than during normal breathing (left). This explains why when deep sleep is interrupted, toxin clearance through the spinal route is impaired.

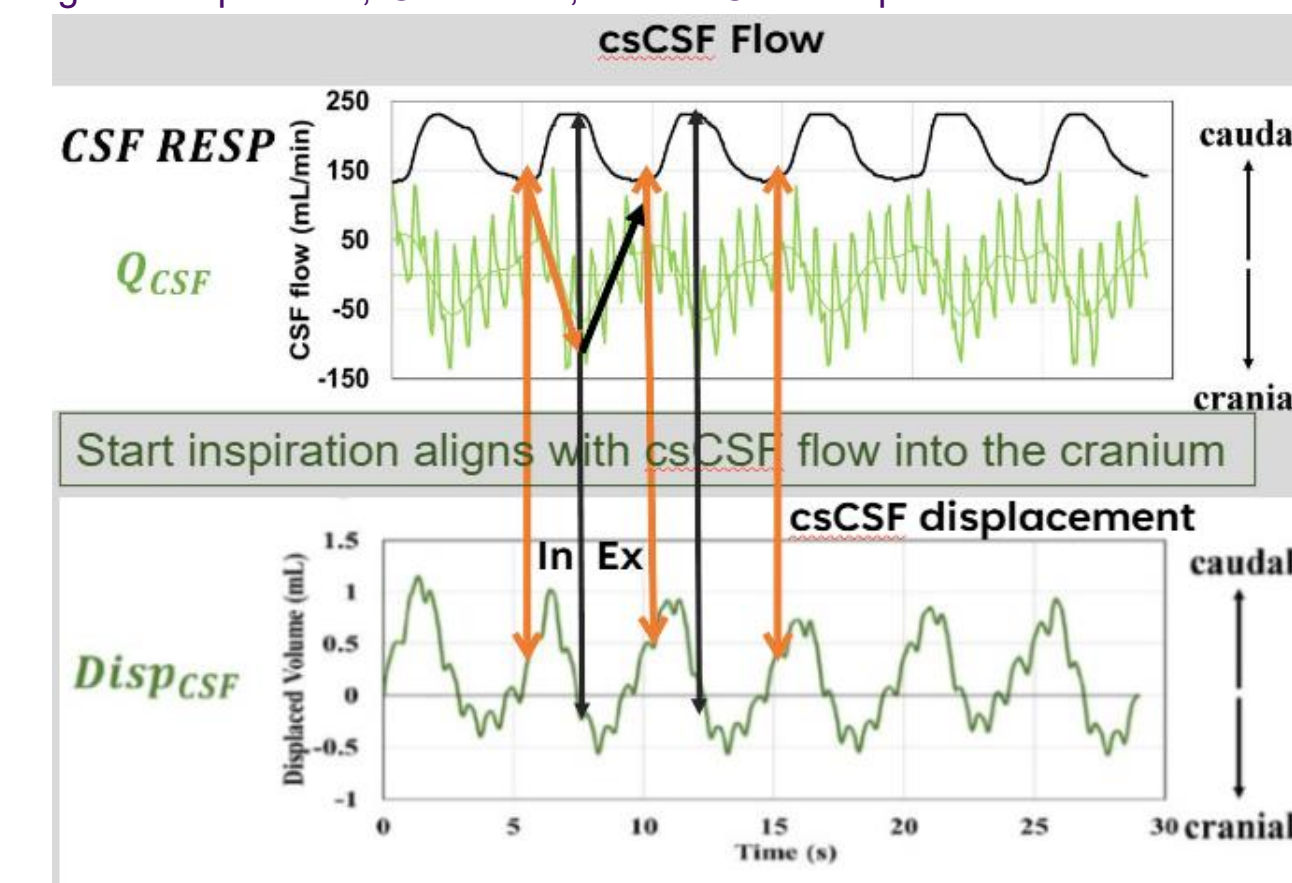


RESULTS

- Relative to NB, SDB increases the maximal displaced csCSF volume by 57%. Breathing pattern during deep sleep amplifies csCSF oscillation and thereby, toxin transfer to spinal csCSF.
- Inspiration generates lower thoracic pressure by thoracic expansion to pull in air. Lower thoracic (and right atrium) pressures increase venous and decrease csCSF outflow.
- Thoracic pressure and volume are inversely related (**Boyle's law**); thus, csCSF flow is inversely related to thoracic expansion (Fig. 4).

$$-\Delta(\text{csCSF}) \propto \Delta(\text{thoracic expansion})$$

Fig. 4 Respiration, CSF Flow, and csCSF Displacement waveforms

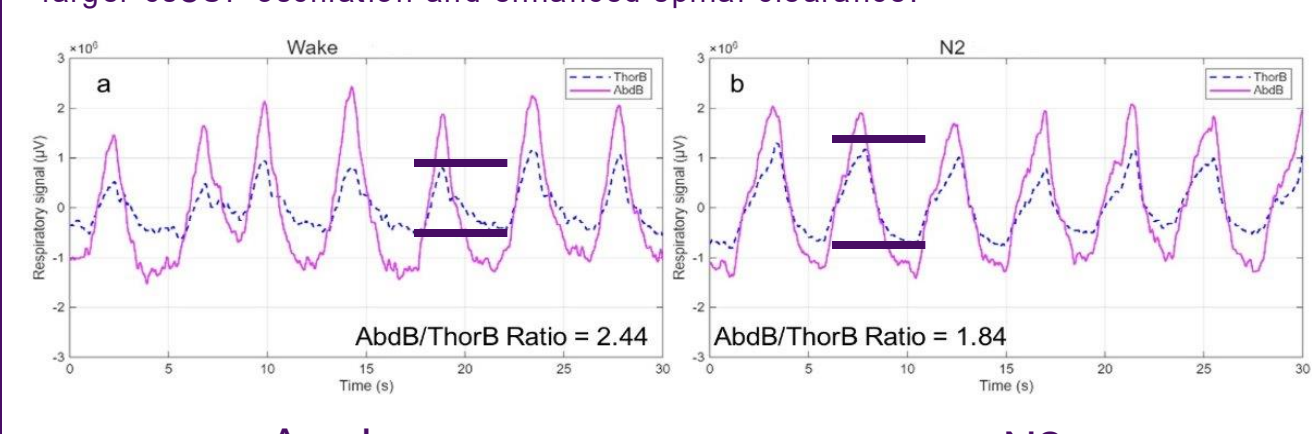


*csCSF displacement is lagging due to inertia.

CONCLUSIONS

- csCSF oscillation is driven by (A-V). Venous outflow (V) is influenced by changes in thoracic and RA pressures during breathing.
- Relative to NB, slow deep breathing resulted in an increased maximal displaced CSF volume during each respiratory cycle.
- In healthy sleepers, spinal clearance may compensate for age-related decline in cranial clearance pathways, while disrupted sleep reduces csCSF oscillations, decreasing spinal clearance and contributing to toxin accumulation.
- Data from our preliminary study shows that abdominal breathing remains similar during wakefulness and N2 sleep, while thoracic expansion increases. Increased thoracic expansion reduces thoracic pressure, thereby enhancing soluble toxin transfer during deep sleep (Fig. 5).

Fig. 5. The effect of sleep stage on abdominal (pink) and thoracic (blue) breathing. Compared to awake, during N2, the thoracic component increases, which implies larger csCSF oscillation and enhanced spinal clearance.



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