Progress Report

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Title of Project: Spinal fluid circulation in the abnormal spinal cord

The brain and spinal cord are bathed in a liquid called cerebrospinal fluid (CSF). CSF is vital to mechanical protection of the central nervous system, as well as to the normal complex function of the brain and spinal cord. It is known that CSF enters the spinal cord and brain where it probably helps to maintain a constant biochemical environment for precise function of brain and spinal cord cells.

Despite the critical role of CSF in some of the body's most important functions, there is only a rudimentary understanding of CSF circulation, especially in the spinal cord. If fluid can enter the spinal cord, then it must also drain out. Although recent research has identified the role of blood vessels in mediating this transport of fluid, many of the details have yet to be clarified. For example, there is still controversy as to the exact arrangement of anatomical compartments around small penetrating blood vessels in which fluid exchange is thought to occur. Forces such as respiration and heart pulsations are thought to be important drivers of fluid flow around and within the spinal cord, and this is another nascent area of research.

Our laboratory group has recently demonstrated for the first time that respiratory generated pressures are the dominant drivers of spinal CSF flow and fluid entry into the spinal cord. Cardiac pulsations contribute to a lesser extent, but are the principal forces in helping fluid drain from the spinal cord. At the microscopic level, we have characterised the hyperdynamic movement of fluid using novel, sophisticated imaging techniques.

In the current project, we aim to examine how CSF flow is different in the disease state, using an animal model of syringomyelia. In syringomyelia, there is an abnormal collection of fluid within the spinal cord that expands and damages the nerve fibres, leading to pain, paralysis, and sometimes, death. It is the endpoint of various conditions such as herniation of brain through the base of the skull (Chiari malformation), spinal cord injuries and tumours, and spina bifida. Although it carries tremendous disability, treatment of syringomyelia often unsatisfactory, which is rooted in an incomplete understanding of how it forms.

This project has been examining spinal CSF flow in syringomyelia models in rodents. In this study we have employed some of the recently developed novel imaging

techniques that allow assessment of fluid flow in the live animal – an important innovation given drivers of CSF are respiration and cardiac pulsations. Under strict blood pressure and respiratory monitoring, “glow-in-the-dark” fluorescent tracers have been injected into the CSF spaces of these animals. The redistribution in the spinal column and into the spinal cord have been studied. We have employed a previously validated model of syringomyelia involving obstruction of the spinal CSF space to reproduce the underlying cause of syringomyelia. This was achieved by tying a ligature around the sac surrounding the spinal cord. We hypothesised that in these animal models of syringomyelia, the flow of CSF would be impeded, with increased accumulation of tracer within the spinal cord tissue.

Although the COVID pandemic has hindered the workflow of our animal experiments, we have been able to investigate how spinal CSF flow differs in the disease model compared to normal animals. There is strong emerging evidence that the flow of spinal CSF is significantly reduced in the syringomyelia state. Moreoever, there is likely less influx of fluid into the spinal cord. This was observed both in cohorts that were being mechanically ventilated, and breathing spontaneously. We are still analysing the results to determine whether spontaneous respiration has additional impact on fluid flow. These results support the prevailing theory that obstruction in the subarachnoid space impedes not only flow of CSF within this compartment, but also fluid exchange across the surface of the spinal cord. It is likely that there is also reduced flow of fluid out from the spinal cord tissue, leading eventually to abnormal accumulation of fluid within the spinal cord. Our next steps are to repeat these experiments in animal cohorts (control and disease state) where increased heart rate and high blood pressures have been induced.

Our efforts to study this enigmatic part of human physiology is part of an endeavour to find better treatments for a neurosurgical condition. However, there is vast potential for translation of this knowledge to other fields such as intrathecal drug systems (delivering cancer treatments to incurable tumours), spinal cord injury and even to neurodegenerative disorders such as Alzheimer’s disease. Disturbance of fluid flow into, and out of tissues of the central nervous system is a likely a common theme in all of these conditions.

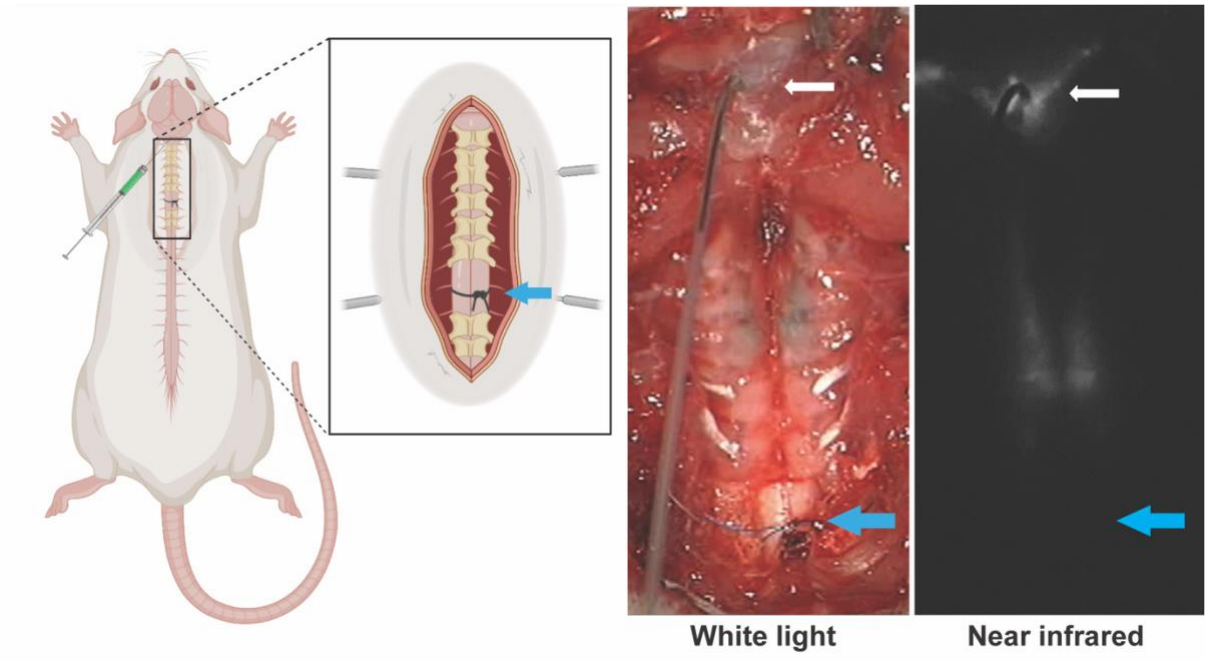

Figure 1 Disease state animal models where CSF flow has been obstructed to simulate syringomyelia (left). Intraoperative view of ligature around spinal cord (middle). Fluoresence imaging of tracer descending down the spinal cord after delivery into the CSF space at the base of the skull (right).

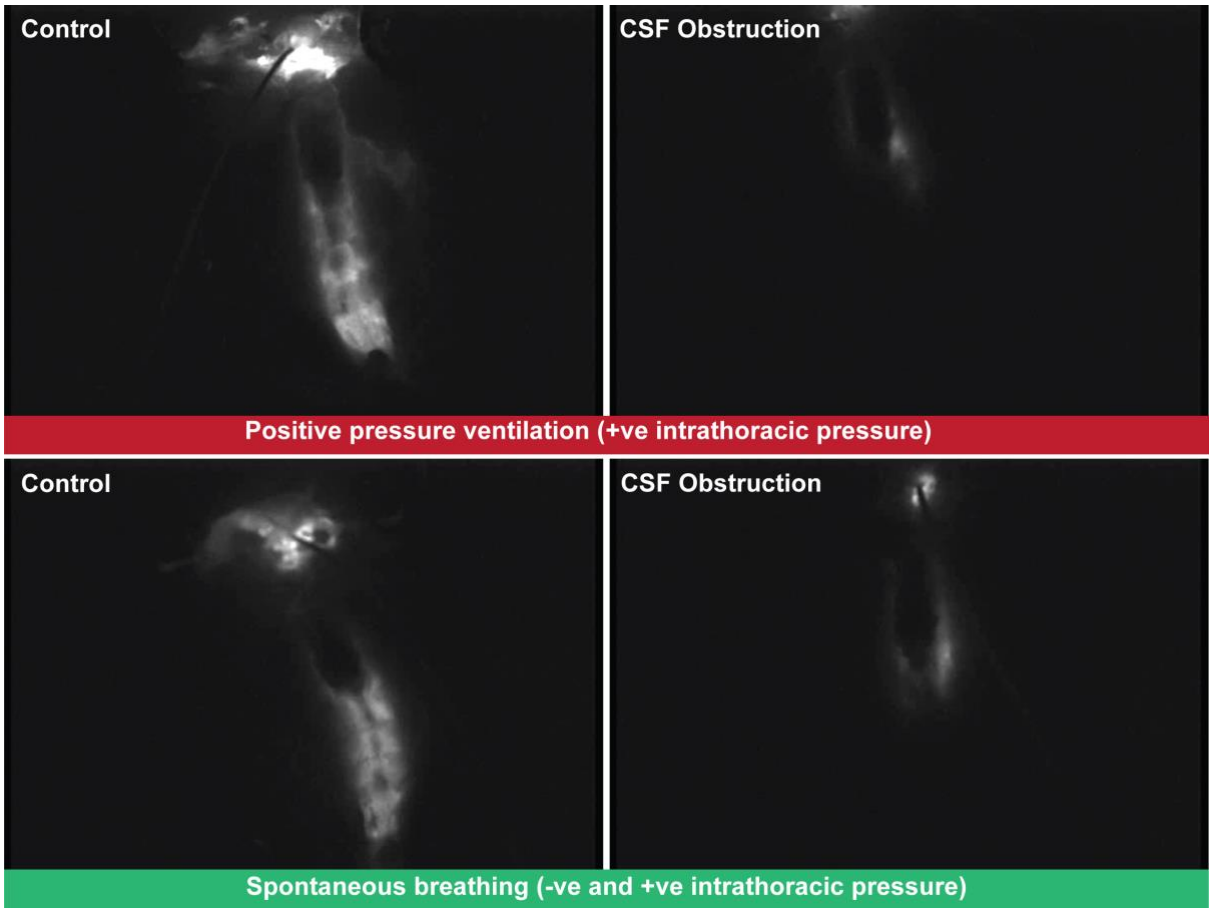

Figure 2 Effect of extradural constriction on spinal redistribution of fluorescent tracer in rats that have been mechanically ventilated and rats that are spontaneously respiring.