

## ORIGINAL ARTICLE

# Closed cranial window rodent model for investigating hemodynamic response to elevated intracranial pressure

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## Abstract

**Background:** Elevated intracranial pressure (ICP) occurs in several physiological and pathological conditions, yet long-term sequelae are not common, which implies that blood flow is preserved above ischemic thresholds.

**Methods:** This pilot study sought to confirm this hypothesis using a closed cranial window model in a rat in which ICP was elevated to 120 mmHg for 12 min, and superficial cortical perfusion was measured by laser Doppler flowmetry and laser speckle flowmetry.

**Results:** Following a transient increase, cortical blood flow decreased to between 25% and 75% of baseline. These levels correspond to disrupted metabolism and decreased protein synthesis but did not exceed thresholds for electrical signaling or membrane integrity. This may partially explain how some episodes of elevated ICP remain benign.

**Conclusion:** The closed cranial window model provides a platform for prospective study of physiologic responses to artificially elevated ICP during neurosurgery to promote hemostasis.

## KEYWORDS

cerebrovascular circulation, craniotomy, hemodynamics, hydrocephalus, intracranial pressure, perfusion

## 1 | INTRODUCTION

The brain is subjected to elevated intracranial pressure (ICP) in several physiological and pathological conditions including idiopathic intracranial hypertension,<sup>1</sup> hydrocephalus,<sup>2</sup> and plateau waves.<sup>3–5</sup> According to the Monro–Kelli doctrine, elevated ICP is offset by a decrease in brain volume via cerebrovascular collapse<sup>6</sup> and may therefore result in reduced perfusion. Nonetheless, long-term functional and cognitive deficits are often not associated with these conditions even though episodes of elevated ICP may approach mean arterial pressure for periods of several minutes or longer.<sup>7</sup> This implies that sufficient

blood perfusion is preserved above ischemic thresholds, but to our knowledge, this hypothesis has not been confirmed experimentally. Therefore, this pilot study aimed to investigate the use of an in-vivo model that permitted real-time measurement of superficial cortical perfusion under prescribed, sustained, and artificially elevated ICP.

## 2 | METHODS

This pilot study was performed under supervision of the Institutional Animal Care and Use Committee (IACUC) of Allegheny General

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Hospital (protocol #895). The study was in compliance with the US National Research Council's Guide for the Care and Use of Laboratory Animals and the US Public Health Service's Policy on Humane Care and Use of Laboratory Animals.

This study utilized a modification to the open cranial window, which directly exposes the brain to atmospheric pressure, by providing a hermetic seal to enable precise control of ICP.<sup>8,9</sup> A custom-made cranial window was installed on an anesthetized rat via surgical procedure, described below. Superficial cortical perfusion was measured by laser speckle flowmetry and laser Doppler before, during, and after application of elevated ICP.

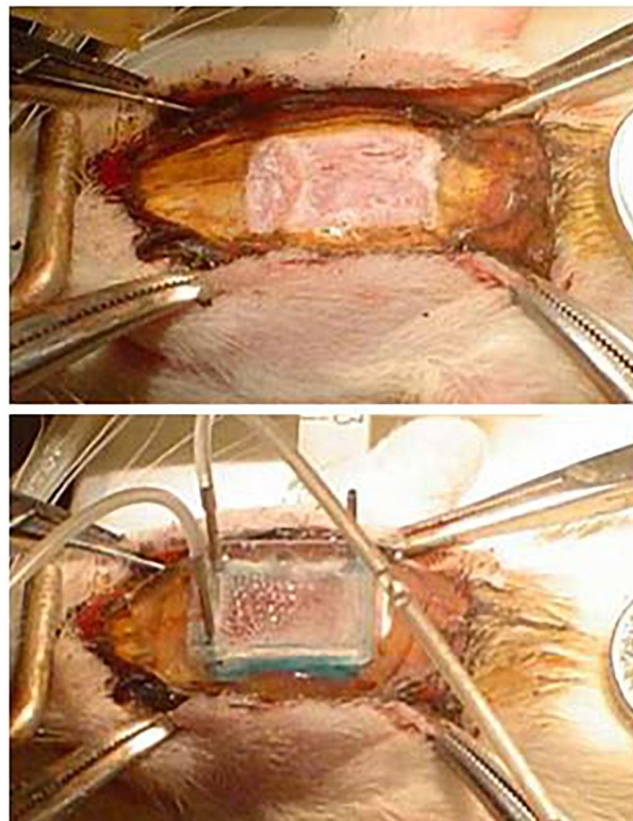
## 2.1 | Surgical procedure

This study utilized a male rat model, commonly used for studying cerebral physiology via cranial windows,<sup>8-12</sup> in which our group has previously reported.<sup>13-15</sup> A single 360-g male Sprague-Dawley rat was anesthetized with isoflurane (4.5% for induction, 1.8%–2.0% during surgery, and 1.0% for maintenance), intubated, and artificially ventilated with 30% O<sub>2</sub> balanced N<sub>2</sub>. End-tidal CO<sub>2</sub> was measured from ventilator exhaust (Datex 223; Puritan-Bennett Corporation; Overland Park, KS). Sufficient anesthesia was regularly assessed via tail pinch test in which elevation of arterial pressure of more than 5% from 100 mmHg indicated suboptimal sedation and dictated an increase in isoflurane. Pancuronium was injected intra-muscularly on a 4 mg/kg/hr basis to repress native ventilation and in turn, control pCO<sub>2</sub> levels and limit blood flow fluctuations due to cerebral autoregulatory responses. Body temperature was maintained at 37°C via servo-controlled heat lamp connected to a rectal probe. A single arterial catheter was inserted in the femoral artery for measuring arterial pressure (DT-XX; Viggo-Spectramed; Oxnard, CA) and for sampling blood gases (iStat<sup>®</sup> Portable Clinical Analyzer with CG8+ cartridge; Abbott Laboratories; Abbott Park, IL).

After placing the animal in a stereotaxic frame in the prone position, a midline scalp incision was created, and the periosteum was removed (See Figure 1). Then, a 1–2 mm foundation of dental acrylic cement was applied to the skull and allowed to cure. The bone tissue within the foundation was thinned with a high-speed grinding tool that was continuously cooled via a jet of air aimed at the site. Bone inside the footprint, but not the sagittal sinus, and dura were removed with forceps. The experiment was terminated by euthanizing the animal via intravenous air embolus following an isoflurane overdose of 5%.

## 2.2 | Cranial window, peripheral equipment, and craniotomy environment

The cranial window was an optically-clear rectangular panel of Plexiglas<sup>®</sup> (12 mm × 8 mm × 1.5 mm, length × width × thickness, respectively) secured to an acrylic foundation on the opened skull via cyanoacrylate, which created a hermetic seal (See Figure 2). Four



**FIGURE 1** The surgical procedure before the craniotomy (top) and after window installation (bottom)

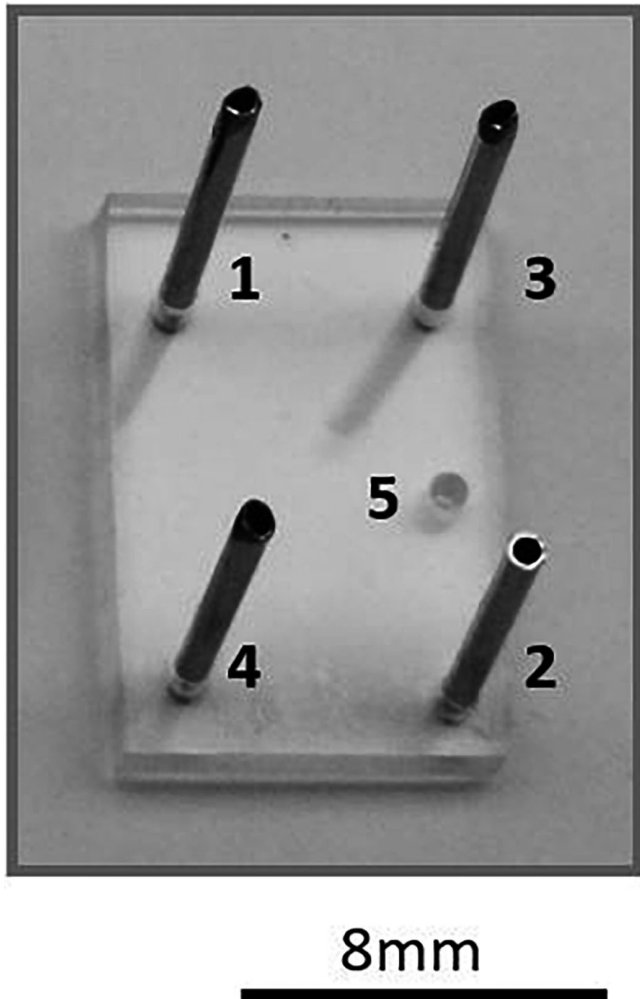
fluid ports at the corners of the window enabled air evacuation, irrigation, and measurement of epicortical pressure. An analog cerebrospinal fluid (aCSF) was prepared as described by Morii<sup>12</sup> (i.e., 7.71 g/L NaCl, 2.07 g/L NaHCO<sub>3</sub>, 0.22 g/L KCl, 0.37 g/L CaCl<sub>2</sub>·2H<sub>2</sub>O, and 0.27 g/L MgCl<sub>2</sub>·6H<sub>2</sub>O) and bubbled with gases (N<sub>2</sub>, O<sub>2</sub>, CO<sub>2</sub>, and isoflurane) in a water bath immersed flask introduced via roller pump to the inflow port at 1.0 ml/min and collected in a hydrostatic reservoir that in turn established the nominal ICP. An additional opening in the window accommodated a thermocouple.

## 2.3 | Elevated ICP

The experimental procedure consisted of raising the hydrostatic reservoir to a height of 1.8 m (approximately 120 mmHg). The pressure was maintained for twelve continuous minutes and then returned to 0 mmHg for an additional 6 min to allow for reperfusion (See Figure 3).

## 2.4 | Data acquisition and image processing

Relative changes in cortical blood flow were measured simultaneously in both hemispheres with laser speckle image flowmetry



**FIGURE 2** The custom-made cranial window with fluid ports for aCSF inflow (#1), aCSF outflow (#2), air evacuation (#3), epicortical pressure application (#4), and thermocouple (#5)

(LSIF) as described by Briers<sup>16</sup> and Boas et al.<sup>17</sup> Briefly, a laser diode ( $\lambda = 780$  nm, 60 mW; Thorlabs; Newton, NJ) and a collimating lens were placed 10 cm above the window to provide uniform illumination of the cortical area. Video recording was accomplished with an 8-bit CCD camera and acquired to computer via a frame grabber with image processing software (LG3 with Scion Image 4.0.3.2; Scion Corporation; Frederick, MD). The exposure time for each LSIF sampling was 15 ms and a sequence of at least five scanned images was acquired at each time point (See Figure 4). A final series of post-mortem LSIF scans were acquired to account for the background signal. Post-processing of the acquired images performed offline with open-source software (ImageJ 1.43u; National Institutes of Health; Bethesda, MD) entailed cropping, background subtraction, and inversion of correlation time to obtain relative velocity.

For direct comparison to published  $\text{CO}_2$  reactivity,<sup>18,19</sup> relative changes in left cortical blood flow were also measured with a clinical laser Doppler flowmeter (BMP-403A; Vasamedics; St. Paul, MN; 780 nm wavelength, 1.6 mW) with Doppler probe (P-433-2) attached to the stereotactic frame. LDF, epicortical pressure, arterial

pressure, and end-tidal  $\text{CO}_2$  were continuously recorded on a personal computer with data acquisition software (WinDaq, DATAQ Instruments Incorporated; Akron, Ohio).

$\text{CO}_2$  reactivity was determined prior to initiation and after completion of the 12-min elevation of ICP. This was accomplished by first recording baseline cerebral blood flow (CBF) and  $\text{PaCO}_2$ , then increasing the  $\text{CO}_2$  in the ventilated gas from 0 to 50 mmHg (~5%  $\text{CO}_2$ ) and recording the resulting CBF and  $\text{PaCO}_2$  approximately 2 min later.  $\text{CO}_2$  reactivity was mathematically defined in terms of the aforementioned parameters as follows:

$$\text{CO}_2 \text{ Reactivity} = \frac{\text{CBF}_{\text{Post}} - \text{CBF}_{\text{Pre}}}{\text{CBF}_{\text{Pre}}(\text{PaCO}_2_{\text{Post}} - \text{PaCO}_2_{\text{Pre}})} \times 100. \quad (1)$$

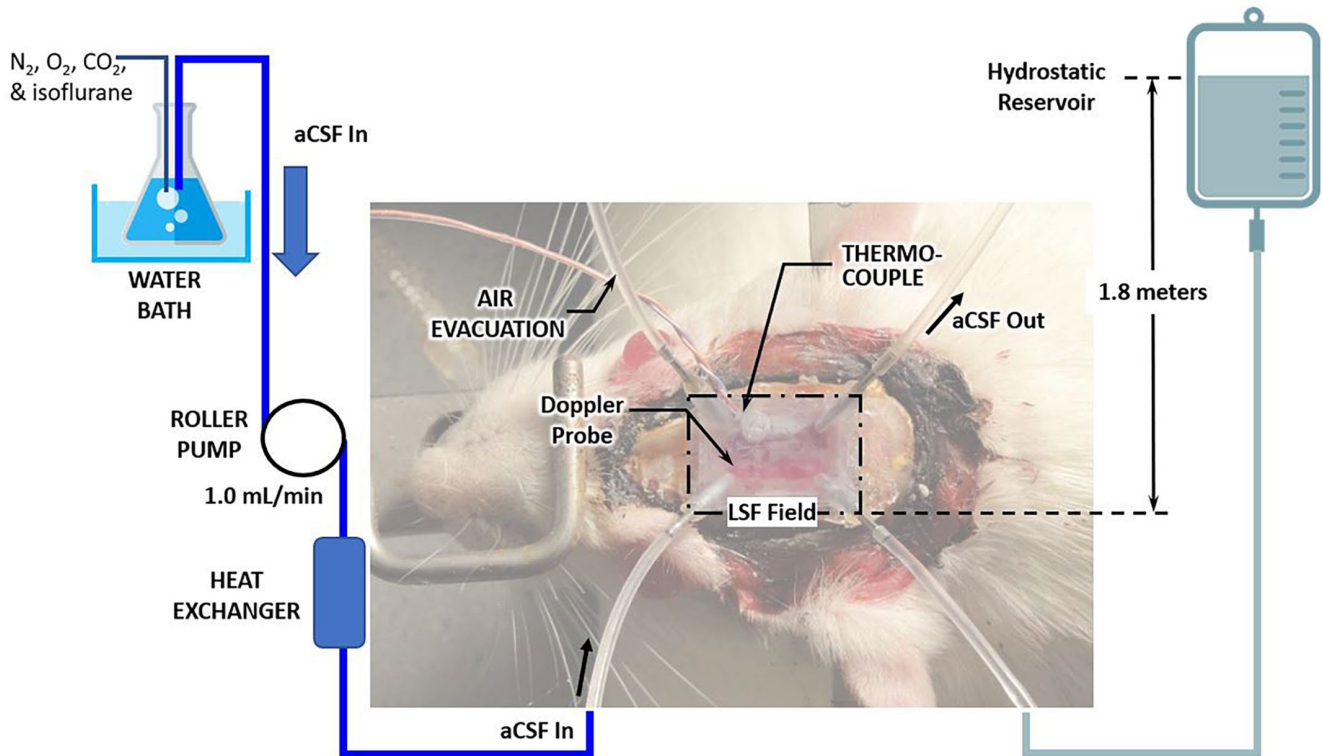
### 3 | RESULTS

Superficial cortical blood flow simultaneously measured by laser Doppler and laser speckle flowmetry in response to elevated ICP is provided in Figure 5. The initial drop in LSF was observed to lag behind the drop in LDF by approximately 3 min. In response to an increase of ICP from 35 to 130 mmHg, superficial cortical blood flows dropped to approximately 50% of baseline, and it took between less than 1 (LDF) and approximately 4 (LSF) min to reach relative stability. After the initial decrease, the flows were observed to rebound for approximately 3 min reaching approximately 60% of baseline in the left hemisphere and approximately 75% of baseline in the right hemisphere. Thereafter, the cerebral blood flows decreased to between approximately 25% and 40% of baseline. During the period of artificially elevated ICP, changes in mean arterial pressure trended with those of cortical blood flow and remained within 10 mmHg of baseline. After ICP was returned to baseline, the cortical blood flow was much less responsive to increased  $\text{CO}_2$ , recorded as a 1.05%/mmHg change in Doppler flow versus 1.33%/mmHg prior to intervention.

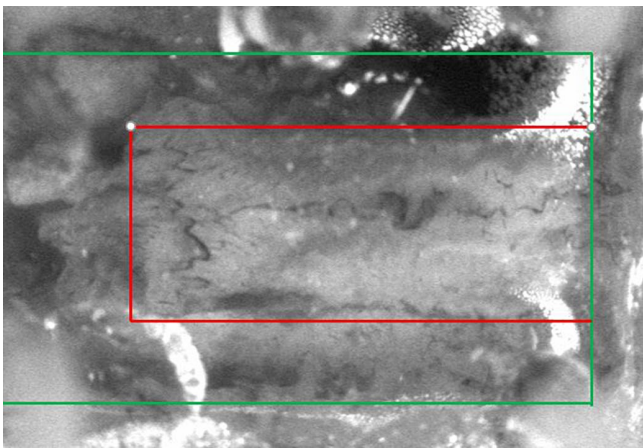
### 4 | DISCUSSION

To our knowledge, this is the first report featuring simultaneously measured, time-varying hydro- and hemodynamic recordings in which ICP was maintained at a level exceeding mean arterial pressure and approaching systolic blood pressure. Various other studies consider the effects of elevated ICP on microvascular perfusion,<sup>20-22</sup> however, these studies report summary values rather than time-varying waveforms, and elevated ICP's are between venous and mean arterial pressures. Therefore, the unique contribution of the study reported here is in elucidating the temporal microvascular perfusion response when ICP is held above mean arterial pressure.

Throughout the 12 min of artificially elevated ICP, superficial cortical perfusion was maintained above 25% of baseline perfusion, which is an ischemic threshold for metabolism according to Lowry et al. (1964) in a murine model.<sup>23</sup> During the period of artificially elevated ICP, superficial cortical perfusion was also sustained above other published thresholds of ischemia that occur at 20 and 10% and



**FIGURE 3** Schematic of the experimental setup. Artificial cerebrospinal fluid (aCSF) was introduced to space beneath the cranial window via roller pump and heat exchanger and maintained at pressure determined by a hydrostatic reservoir. LSF indicates viewing region for laser speckle flowmetry



**FIGURE 4** Representative laser speckle image with the anterior to the left and the foundation around the top, right, and bottom perimeter (outside the green lines). The sagittal sinus (inside the red lines) is intact from the right center to bregma, left of center. The cortex is exposed on the left and between the foundation and sagittal sinus (outside the red and inside the green lines)

correspond to loss of electrical signaling and membrane failure, respectively.<sup>24</sup> Therefore, high ICP exceeding mean arterial pressure and approaching systolic blood pressure may allow some physiologic processes to proceed, albeit attenuated. This may partly explain why idiopathic intracranial hypertension, hydrocephalus, and plateau

waves do not usually cause long-term deficits. However, when such conditions result in perfusion below 50% of baseline, protein synthesis may be suppressed.<sup>24</sup>

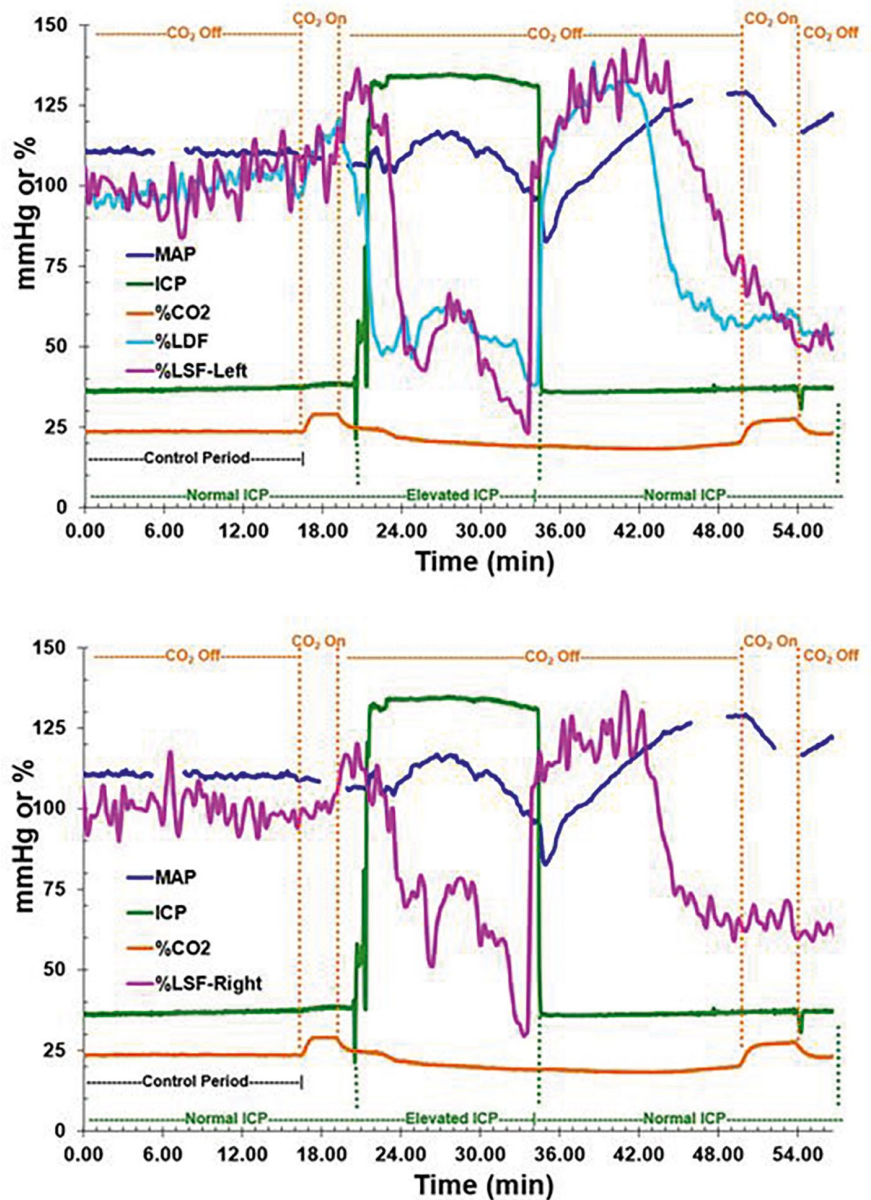
Upon initiation of high ICP in this experiment, flow decreased by half, which was potentially due to venous collapse, particularly of large superficial venous structures such as the sagittal sinus. This is consistent with previous findings in a primate model in which ICP was raised above 70 mmHg, and cerebral blood flow trended towards less than half of baseline.<sup>25</sup> The in vivo data here are also consistent with those of our previously published benchtop model in which extravascular pressure being raised to half of mean arterial pressure resulted in flow becoming approximately half of baseline.<sup>26</sup>

Arguably the most striking observation in this experiment was that superficial perfusion remained consistently above zero despite ICP approximating systolic blood pressure. This could be explained by intermittent forward flow during the portion of the cardiac cycle in which systolic arterial pressure exceeded ICP. A second contributing factor could be that deeper vessels are less susceptible to superficial pressure and hence remain patent due to tethering or shielding by surrounding tissue. This hypothesis is supported by prior benchtop studies demonstrating the effect of tethering on vessel collapse in response to extramural pressure.<sup>27-30</sup>

Between 3 and 6 min after initiation of artificially elevated ICP, there was a simultaneous increase in blood flow and MAP, which may be attributable to the Cushing response.<sup>31</sup> The response was observed in both hemispheres and by both modes of cerebral blood



**FIGURE 5** Superficial cortical blood flow as simultaneously measured by laser Doppler (LDF, light blue) and laser speckle flowmetry (LSF, purple) in response to prescribed profiles of artificially elevated intracranial pressure (ICP, green) and carbon dioxide ( $\text{CO}_2$ , orange). ICP and  $\text{CO}_2$  were universally applied; however, blood flows were measured more locally. Laser Doppler flowmetry was only acquired from the left hemisphere whereas laser speckle flowmetry was independently and simultaneously sampled from the left (top) and right (bottom) hemispheres. Mean arterial pressure (MAP, royal blue) was also measured throughout the experiment



flow measurement suggesting a global rather than a local phenomenon. Symmetric distribution of blood flow also suggests that pressure was evenly distributed throughout the subarachnoid space, as previously shown in a primate model.<sup>32</sup>

Doppler  $\text{CO}_2$  dynamics were previously shown to be an indicator of vascular reactivity,<sup>19</sup> and this method has been utilized in a rat model.<sup>13</sup> Here, the pre-intervention  $\text{CO}_2$  reactivity test demonstrates that the surgical procedure did not damage vascular control mechanisms while the diminution of  $\text{CO}_2$  reactivity post-intervention suggests that these vascular control mechanisms were partially impaired. Further studies assessing impairment of vascular control mechanisms due to artificially elevated ICP magnitude and duration would be valuable to better understand the hydro- and hemodynamic interplay observed during clinical conditions of elevated ICP. This experiment draws some analogy to idiopathic intracranial hypertension, hydrocephalus, and plateau waves, and direct

association to any specific clinical condition could be accomplished in additional experiments by employing more specific hydro- or hemodynamic profiles characteristic of these conditions. For example, extension of this pilot study to investigation of plateau waves could be accomplished by applying a series of six episodes of ICP between 50 and 100 mmHg for 20 min at intervals of 30 min.<sup>33</sup>

Artificially elevated ICP through a closed aqueous environment has been proposed as a means to control hemorrhage during brain surgery.<sup>26,34,35</sup> This hypothesis is supported by observations from this pilot study inasmuch as rapid increase of ICP to near systolic blood pressure levels did not attenuate superficial cortical perfusion to a low equilibrium but rather steadily declined over the course of minutes. If reliably established, such a delayed response may be leveraged to create a system in which the surgeon could artificially raise ICP long enough to suppress hemorrhage and clear the visual field while not critically compromising perfusion. The

delay in responsiveness between LDF and LSF requires further examination. This pilot study has several limitations. The currently configured system is only capable of quantifying superficial perfusion; therefore, the effects of artificially elevated ICP on blood flow in deeper regions of the brain cannot be assessed via these methods. Although superficial perfusion was measured, corresponding observations were not made about changes in superficial vascular structures such as the superior sagittal sinus, and as a result, it can only be theorized that these structures collapsed due to artificially elevated ICP. Additional techniques may be necessary to fully capture cerebral vascular responses to various profiles of artificially elevated ICP.

## 5 | CONCLUSIONS

This pilot study demonstrated the use of a closed cranial window model to assess the effect of sustained elevated ICP on superficial perfusion. Cortical blood flow, measured via laser Doppler and speckle tracking flowmetry during a 12-min episode of 120 mmHg, revealed sustained superficial cortical perfusion above thresholds of ischemia. This finding motivates further investigation of the role of the structure of cerebral vasculature on hemodynamic regulatory mechanisms and the physiologic responses to anomalies in ICP. These results also support future investigation into the safety and efficacy of artificially elevated ICP as a means of promoting hemostasis during neurosurgery.

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## CONFLICT OF INTEREST

The authors declare that they have no conflicts.

## AUTHOR CONTRIBUTIONS

MTO was involved with all phases of the project including design, experimentation, data analysis, writing, editing, and grant funding (40%). JFA reviewed data, wrote, and edited (30%). AK assisted with experimentation and data analysis (15%). SCJ provided overall intellectual support and laboratory resources (15%).

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