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TOPICAL REVIEW

Hypertension, blood–brain barrier disruption and changes in intracranial pressure

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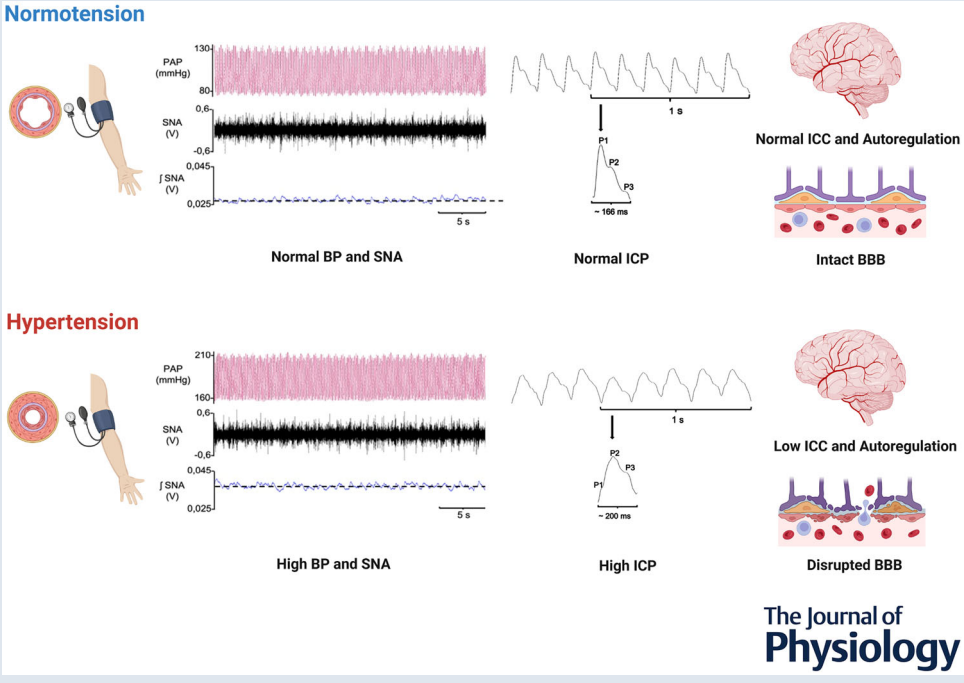

Abstract figure legend The schematic abstract illustrates how chronic hypertension disrupts neurovascular control, leading to abnormal intracranial pressure (ICP) regulation and blood–brain barrier (BBB) breakdown, which are the key contributors to cerebrovascular disease. In normotensive conditions (top panel, blue), arterial blood pressure (PAP) and sympathetic nerve activity (SNA) remain normal, resulting in a typical ICP waveform where P1 is higher than P2 and P3, which reflects intact intracranial compliance and preserved BBB integrity. In contrast the hypertensive state (bottom panel, red) is marked by elevated PAP, increased baseline SNA and significant ICP waveform alterations – including a prolonged duration and an inverted P1/P2 pattern (P1 < P2) – indicative of intracranial hypertension and reduced compliance. These changes compromise cerebral autoregulation and BBB function, increasing vulnerability to neurovascular damage and contributing to cerebrovascular pathology.

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Introduction

Imagine a silent, relentless force within the skull exerting pressure, which can mean the difference between life and death. This force, intracranial pressure (ICP), is a critical yet often overlooked factor in cerebral health and disease. ICP is the pressure within the cranium, a closed compartment that confines three main components: the brain tissue, blood and cerebrospinal fluid (CSF). According to the Monro-Kellie doctrine ICP dynamics depend on the constant equilibrium of these three components (Harary et al., 2018; Kazimierska et al., 2021). Blood flow is crucial in maintaining this state, and the pressure levels within the vessels that carry arterial blood into the brain and those that drain it through the cerebral venous system must be considered. Another factor affecting this balance is the production and reabsorption of the CSF. Under normal circumstances ICP in a supine human adult ranges between 5 and 15 mmHg, maintaining a delicate balance between cerebral perfusion and the flow of interstitial fluid (ISF) and CSF (Czosnyka & Pickard, 2004; Ursino & Lodi, 1998). An imbalance or a quantitative change in the volume of any cranial component may affect the pressure levels within the cranial cavity. When this balance is disrupted by conditions such as cerebral haemorrhage, hydrocephalus, ischaemia-reperfusion injury and malignant hypertension, the resulting increase in ICP can devastate the brain or even prove fatal (Ursino & Lodi, 1998). Intracranial compliance (ICC) is an essential element of cerebral accommodation, and various diseases can lead to alterations in this relationship. ICC refers to the capacity inside the cranium to accommodate additional volume without a substantial increase in ICP; that is, it represents the change in volume (ΔV) per unit change in pressure (ΔP). ICC is a valuable indicator of the brain's ability to adapt to changes in intracranial volume and may be impaired in pathological conditions such as hypertension (Donnelly et al., 2019).

Systemic arterial hypertension is a critical global health condition. It is defined as an increase in pressure levels within arteries that occur systemically throughout the body. The numerical values of the pressure exerted by the blood against the arterial walls during cardiac contraction and relaxation (systolic and diastolic pressures, respectively) were evaluated for clinical parameters. These measurements can be taken casually in a clinic or through home monitoring methods such as ambulatory or home blood pressure monitoring (Oparil et al., 2018). The prevalence of hypertension continuously increases due to several factors, including population ageing and greater exposure to modifiable lifestyle risks (Mills et al., 2020). There is a strong correlation between hypertension and cerebral disease. Over the years microvascular damage in the brain due to elevated pressure levels leads to lesions in the blood–brain barrier (BBB), white matter and basal ganglia. These are often asymptomatic in the early stages but can cause cognitive, motor and behavioural deficits later in life (Faraco & Iadecola, 2013; Gorelick et al., 2017). Such individuals are at increased risk of lacunar infarcts (Marcolini et al., 2019). Acute cerebral events such as cerebral haemorrhage can also be associated with hypertension. In these cases patients with long-standing hypertension may develop lipohyalinosis and rupture of small vessels, leading to haemorrhages in deep brain structures and ventricular spaces. Depending on the volume of bleeding, it can progress to intracranial hypertension (IH). Hypertension-induced variations in cerebral blood volume (CBV) produce oscillations within the cerebral vasculature, substantially influencing the ICP. IH, which may be, among others, a secondary complication of systemic hypertensive disease, can lead to cerebral dysfunction and mortality due to mechanical distortion and obstruction of cerebral blood flow (CBF) (Elliott, 2007; Fuchs & Whelton, 2020; Sharma et al., 2024).

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Additionally hypertension-induced changes in blood pressure can affect the size of the cerebral vascular compartments, potentially influencing ICC, especially during periods of decompensation. Mounting evidence suggests that many cerebrovascular disorders could be triggered by hypertension. These disorders range from prominent stroke events to mild subclinical cerebrovascular abnormalities, which significantly increase the risk of cognitive impairment (Cipolla et al., 2018; Dean & Shuaib, 2011; Ungvari et al., 2021). Several lines of evidence point to a relationship between hypertension and ICP (and ICC), but the mechanisms underlying this link are still limited.

IH is defined as an increase in pressure within the cranial cavity, which is influenced by the balance between cerebral perfusion and the production and absorption of CSF and ISF. IH is specifically characterized by a sustained ICP elevation exceeding 20 mmHg for >5 min. Non-invasive and invasive monitoring of ICP wave morphology enables the assessment of changes in ICC and the identification of IH through quantitative/qualitative parameters such as the P2/P1 waveform ratio (Fernandes et al., 2021). The waveform associated with ICC consists of three peaks, P1 and P2, corresponding to the systolic peak of the systemic arterial pressure, cerebral arterial volume and venous blood flow, respectively. The P3 is of lesser importance as it relates to the dicrotic notch. However, the relationship between P1 and P2 varies with cerebral compliance; typically P1 is higher, but as compliance decreases, P2 increases. This makes the P2/P1 ratio a crucial metric for such evaluations (Fernandes et al., 2021).

Therefore this review aimed to provide a better understanding of the intricate connection between systemic hypertension and ICP regulation. We focused on the mechanisms underlying ICP and ICC adjustments observed in acute and chronic hypertensive conditions. In addition we discuss current evidence indicating that inappropriate ICP and ICC adaptations in response to high blood pressure levels may contribute to different types of brain dysfunction observed in hypertension and also contribute to a further increase in blood pressure.

Hypertension

Hypertension has a complex pathogenesis involving numerous factors and dysfunction of the cardiovascular system. Beyond being a leading risk factor for mortality worldwide, systemic hypertension predisposes individuals to heart disease, kidney failure and cerebrovascular accident. It is currently estimated that approximately 1.28 billion adults aged between 30 and 79 years are hypertensive, with ∼46% being unaware of their condition (WHO, 2021). However awareness and control are crucial, as hypertension remains one of the leading causes of premature death worldwide (Colombari et al., 2001; Gupta et al., 2020; Wilson et al., 2020). Arterial hypertension is characterized by a sustained increase in blood pressure over extended periods, with levels consistently exceeding 130–139 mmHg/80–89 mmHg at stage 1 and >140/90 mmHg at stage 2 (Whelton et al., 2018).

Failure to control high blood pressure can result in a range of severe consequences for the body, including significant damage to the heart and cardiovascular system. Excessive pressure causes arterial thickening, which reduces the blood flow and decreases the amount of oxygen distributed throughout the body. One direct outcome of this is heart attack, as impaired blood flow to the heart leads to cell death due to oxygen deprivation. Additionally high blood pressure can result in heart failure if the heart is damaged and is unable to pump sufficient blood to meet the body's needs. Another common consequence of high blood pressure and arterial blockage is a reduced supply of blood and oxygen to the brain, which can lead to stroke, depending on its severity. It is also important to note that hypertension can cause kidney damage, which may progress to kidney failure (Ettehad et al., 2016; Vogt et al., 2023).

The development of arterial hypertension involves several contributing factors, with hyperactivity of the sympathetic nervous system (SNS) and renin–angiotensin–aldosterone system (RAAS) being particularly significant. For instance SNS is well documented to be elevated before the onset of hypertension and is directly implicated in the pathophysiology of hypertension among younger individuals (Grassi et al., 2015; Simms et al., 2009). The hyperactivity of the SNS not only initiates but also perpetuates high blood pressure, leading to thickening of arteries, reduced blood flow and insufficient oxygen delivery to critical organs. This ongoing process can result in serious health outcomes such as cardiovascular and kidney diseases. These insights highlight the importance of addressing the underlying mechanisms driving hypertension, underscoring the crucial need to manage hypertension and maintain overall cardiovascular health (Grassi et al., 2015).

Furthermore the BBB is compromised in cardiovascular diseases. Studies from our laboratory and others have shown that the BBB ruptures in the case of neurogenic hypertension. For instance experimental animal models, such as spontaneously hypertensive rats (SHRs) and rats with renovascular hypertension, have been shown to possess a compromised BBB (Biancardi et al., 2014; Fernandes et al., 2021). Similarly some studies have shown that Dahl salt-sensitive hypertensive rats have a ruptured BBB in regions such as the corpus callosum and hippocampus (Pelisch et al., 2011). Interestingly the BBB is also affected in the early stages of hypertension, and both the ICP and P2/P1 index exhibit changes at the onset of the condition (Fernandes et al., 2021).

ICP and ICC

History. The history of ICP measurement can be traced back to the 19th century. In 1866 Salomon Henschen pioneered this field by defining the concept of ICP using a water manometer connected to a hole in the skull for brain pressure monitoring (Ropper, 2009). This early method laid the groundwork for understanding ICP under various neurological conditions. In 1960 Nils Lundberg's classification system marked a significant advancement in ICP monitoring (Lundberg, 1960). The system categorized 'A', 'B' and 'C' waves of ICP, offering a framework for studying ICP in different neurological disorders. The shape of these waves may vary under various circumstances, and distinct ICP patterns may provide crucial information on the brain pathophysiology. Advanced technologies in the mid-20th century further improved the standardization of ICP measurement techniques, enhancing their accuracy and reliability, which, in turn, aided in the monitoring and managing patients with neurological disorders. In this scenario a study by Miller et al. established a relationship between high ICP levels and adverse health outcomes, highlighting the importance of early detection and management of IH (Miller et al., 1977). Miller's advocacy for ICP monitoring led to its inclusion in the Brain Trauma Foundation guidelines (Carney et al., 2017), underscoring the importance of monitoring ICP in managing traumatic brain injuries.

ICP measurement. ICP measurement has a long history, with technological advancements enabling continuous monitoring, crucial for timely intervention and improved outcomes (Chen et al., 2014). Various factors, including body position, respiratory mechanics and CBF, can affect ICP and ICC (Klarica et al., 2014; Sagirov et al., 2023). For example maintaining adequate cerebral perfusion while reducing ICP prevents cerebral ischaemia (Convertino et al., 2011). Studies have demonstrated that changes in body position can affect cerebrovascular circulation, venous outflow and CSF dynamics, thereby influencing ICP and ICC (Sagirov et al., 2023).

Adaptation mechanisms in response to changes in ICP and ICC are vital for preserving brain functions. Increased ICP can diminish the pulsatile component of cerebral venous outflow, thereby affecting cerebral perfusion (Unnerback et al., 2019). Furthermore alterations in physiological variables, such as CBF, mean arterial pressure (MAP) and jugular venous oxygen saturation, can affect outcomes in brain injuries (Struchen et al., 2001). Understanding these relationships is essential for optimizing patient care and outcomes in neurocritical conditions.

ICC plays a crucial role in regulating ICP and preventing cerebral damage. Impairment in the ICC can lead to a loss of compensatory reserve, indicating a reduced ability of the brain to accommodate volume changes without a significant pressure increase (Brasil, 2022). Studies have emphasized the importance of monitoring ICP pulse morphology as a potential indicator of ICC impairment (Brasil, 2022). Additionally computational models have been developed to simulate pressure and volume changes within cerebral compartments, offering insights into cerebral oedema and its related pathophysiology (Doron et al., 2021).

The relationship between ICP and cerebral physiology is complex and multifaceted. Factors such as CSF dynamics, BBB function and CBF regulation contribute to maintaining normal levels of ICP and ICC (Doron et al., 2021). Studies have also investigated the impact of interventions such as positive end-expiratory pressure and prone positioning on cerebral physiology, underscoring the need for personalized approaches in neurocritical care (Corradi et al., 2018). Furthermore advancements in computational modelling and non-invasive measurements have enhanced our understanding of intracranial dynamics and their implications for brain health (Vandenbulcke et al., 2022; Wang et al., 2019).

CBV changes significantly influence ICP. Increased CBV can lead to an increase in ICP, particularly when cerebral compliance is reduced (Parma et al., 1993; Ursino & di Giammarco, 1991). CBF and CBV are closely related but can change independently. Changes in CBF are generally more pronounced than those in CBV under various conditions. For instance during hypocapnia, hypercapnia and hypoxaemia, the percentage changes in CBF were found to be greater than those in CBV (Fortune et al., 1995). This difference is particularly notable during hypocapnia induced by hyperventilation, suggesting that therapeutic hyperventilation may impair CBF to a greater degree than it reduces ICP.

Interestingly the relationship between CBV, CBF and ICP can be complex and depend on various factors. In patients with intact autoregulation lowering blood pressure can cause a steep increase in ICP, whereas increasing blood pressure may not affect ICP. However in patients with defective autoregulation, ICP varies directly with blood pressure (Bouma et al., 1992). These findings highlight the importance of considering individual patient characteristics and autoregulatory status when managing ICP in clinical settings.

Six decades have passed since the delivery of neurosurgeon Nils Lundberg's dissertation on ICP monitoring, highlighting a significant milestone in its clinical incorporation. ICP surveillance has now become a standard practice globally, serving as a fundamental component in the surveillance of patients with acute brain injuries or diseases, as well as aiding in the diagnosis of individuals with chronic neurological conditions. Despite

this widespread adoption a debate exists regarding the indications, clinical relevance and overall significance of different ICP metrics. In our critical evaluation we examined the constraints and deficiencies of current approaches to ICP measurement, whether invasive, minimally invasive or non-invasive. Studies exploring novel technologies for ICP monitoring emphasize the importance of viewing ICP not only as a numerical value but also as a parameter that correlates with ICP morphology alongside various cardiovascular and respiratory parameters. This comprehensive approach offers a deeper insight into the dynamic evolution of intracranial cerebral compliance moment by moment and beat by beat. Outside intracranial equilibrium the CNS controls all integrative systems governing overall bodily harmony.

Consequently the harmonious integration of both circuits is imperative under physiological and pathophysiological circumstances. Although the literature extensively covers the risks associated with the invasiveness of ICP monitoring, it is crucial to highlight additional limitations in existing ICP measurement technologies. These limitations include challenges related to ensuring the quality of the ICP signal source and fluctuations in the zero-pressure reference level, leading to variations in the mean ICP readings and derived indices. Ensuring the reliability of the ICP source signal is critical for non-invasive and minimally invasive ICP measurement. Integrating various signals into a single monitoring system is envisioned as a future direction, necessitating a concerted effort to address the current shortcomings of present-day ICP modalities to enhance the clinical efficacy of ICP monitoring as the gold standard for diagnostic and therapeutic purposes. Numerous experts regard continuous ICP monitoring as essential for monitoring and diagnosing neurological and neurosurgical patients. However specific facets of ICP monitoring are contentious, including issues such as the clinical criteria for ICP utilization, the predictive role of ICP in clinical outcomes of diseases or treatment strategies, the practical value of different ICP metrics and the optimal methods for ICP measurement. Despite the evolution of clinical practice over the past 60 years, the ongoing debate persists.

Analysis of ICP waveform. Brain compliance is calculated using the equation $C = \Delta V/\Delta P$. To study this parameter it is necessary to cause changes in volume and, consequently, obtain changes in pressure. Various approaches have emerged over time. Miller et al. proposed the volume–volume–pressure response, which is the change in ICP caused by adding 1 ml of liquid to the CSF space. Later in 1970 Katzman and Hussey proposed an infusion test and bolus injection technique (Marmarou et al., 1975). Recently the computerized infusion test has emerged as a modern version of the infusion test proposed in the 1970s (Borgesen et al., 1992). The infusion of known volumes at specific times allows for complex and detailed analyses of brain parameters, particularly compliance. Estimating compliance through infusion is considered the gold standard and the only way to measure compliance in millilitres per millimetre of mercury.

Although most of the time ICP monitoring is clinical and direct, it is possible to obtain a great deal of important information in addition to quantitative information (Czosnyka et al., 2007; Kirkness et al., 2000; Wagshul et al., 2011). The waveform itself can provide relevant data on cerebrospinal pressure–volume compensation. The wave reflects the blood and surface volume fluctuations in each cardiac heartbeat. Thus the changes observed in the ICP signal are always synchronized with the heart rate (Ambarki et al., 2007).

In the ICP wave it is generally possible to observe three maximum points, called peaks P1, P2 ('tidal wave' reflecting brain compliance) and P3, with P2 and P3 separated by the dicrotic notch (Germon, 1988). However the morphology of the wave can be altered, such that P2 and P3 tend to increase if the mean ICP increases (Castel & Cohandon, 1976; Fernandes et al., 2021; Gega et al., 1980).

There appears to be a relationship between arterial and venous peaks and factors with volume and pressure relationships inside the skull (Dardenne et al., 1969). The P1 peak is related to the systolic peak of blood pressure, which is related to pulse propagation and arterial distension (Carrera et al., 2010; Fan et al., 2008). In turn the P2 and P3 peaks involve changes in the brain volume and compensation. P2 is significant because it synchronizes with the maximum cerebral arterial volume (Carrera et al., 2010).

Therefore the morphology of the ICP waves can provide important information on an individual's health. When the ICP values are low, the three peaks form an ascending pattern, with P1 being the most prominent (Castel & Cohandon, 1976; Gega et al., 1980; Portnoy & Chopp, 1981). However if there is an increase in the mean ICP values, there is an increase in ICP pulsatility, and the peaks become increasingly less defined. Thus with extreme increases the wave turns parallel with the shape of a single peak (Czosnyka & Citerio, 2012). It is possible to assess impairment in brain compliance by analysing the P2/P1 ratio. That is when the P2 peak exceeds the P1 peak, the ICC becomes compromised (Brasil et al., 2021; de Moraes et al., 2022).

In the event of an increase in intracranial volume and exhaustion of all regulatory mechanisms, there is an increase in ICP values and waveform deformation so that P2 assumes higher values than P1 (Fan et al., 2008). In a study conducted by our group (Fernandes et al., 2021), using invasive and non-invasive ICP monitoring, the morphology of the ICP wave was analysed during the

development of renovascular hypertension [2 kidney-1 clip model (2K1C)] in rats. Initially in the first week after surgery, P1 was greater than P2; however after the third week the relationship was reversed, and P2 became greater than P1. This shows that in renovascular hypertension, the morphology of the ICP waves changes.

Importance of ICP measurement in pathology. ICP and ICC are crucial physiological factors that have a substantial impact on brain function and health, as previously mentioned. The quantities of brain tissue, fluid between brain cells, CSF and blood in cranial arteries collectively determine ICP (Canac et al., 2020; Roy & Sherrington, 1890). This explains the correlation between cerebral perfusion and the production and removal of ISF and CSF, with typical values ranging from 5 to 15 mmHg (Czosnyka & Pickard, 2004; McBryde et al., 2017). Severe ICP elevation can result from malignant hypertension and many other disorders, such as brain trauma (Canac et al., 2020; Schwartz, 2002). An elevated ICP directly leads to a decrease in cerebral perfusion pressure (CPP) and brain compliance. This can cause cerebral ischaemia or herniation, resulting in impairment and higher mortality rates (Czosnyka & Pickard, 2004; Helbok et al., 2014; Treggiari et al., 2007). Conversely ICC refers to the capacity of the brain to adapt to changes in volume without a substantial increase in pressure (Brasil, 2022). Intracranial elastance, also known as ICC when its inverse is included, has been proposed as a valuable addition to the interpretation of ICP and as a means to provide a more accurate description of brain homeostasis (Ocamoto et al., 2021). ICC is associated with compensatory mechanisms that maintain ICP stability. The degree of compensation determines how well the intracranial content can adjust to variations in volume and pressure (Harary et al., 2018). Czosnyka and Citerio proposed that ICC is a complex function that depends on the interaction between venous, CSF and arterial compartments. This relationship is influenced by various vascular factors, including the regulation of CBF, tension of arterial smooth muscles, partial pressure of CO_2, endothelial function, brain hydration and metabolism (Czosnyka & Citerio, 2012). Comprehending these principles is essential for effectively addressing disorders such as hydrocephalus, traumatic brain injury and cerebral ischaemia.

ICP adaptation mechanisms. The primary mechanism of ICP adaptation to acute systemic hypertension is autoregulation, which is essential for maintaining cerebral homeostasis. This phenomenon occurs when the brain effectively controls the diameter of the cerebral resistance arteries to maintain the flow of blood in the brain within a specific range of MAP or CPP, which is the difference between MAP and ICP (Paulson et al., 1990; Silverman & Petersen, 2024). However this innate ability to regulate itself is diminished in cases of hypertension, whether sudden or long-lasting. Acute hypertensive crises occur when there is an excessive quantity of blood flow in the brain that surpasses its ability to regulate itself. This leads to a clinical condition known as hypertensive encephalopathy (Mann, 2008). Several factors, such as cerebral oedema, IH, cerebral ischaemia caused by vascular spasm and damage to the BBB, have been identified as contributing to the development of hypertensive encephalopathy (Bar, 2017; Potter et al., 2024; Price & Kasner, 2014; Sharifian, 2012).

In cases of chronic systemic hypertension, the brain adapts by shifting the autoregulation curve to the right, indicating that more significant changes in systemic blood pressure are necessary to alter CBF. This adaptation allows the brain to tolerate higher blood pressure without a corresponding increase in ICP. However this also means that a sudden decrease in blood pressure can severely compromise CBF and cause cerebral ischaemia (Strandgaard & Paulson, 1984). Simultaneously chronic hypertension leads to the alteration of the structure of blood vessels in the brain, specifically resulting in thickening of the middle layer, narrowing of the inner space, decreased ability of the arteries to relax and impaired functioning of the inner lining of the blood vessels. These traits combine to establish an adaptable reaction that broadens the autoregulatory spectrum (Pires et al., 2013).

Relationship between ICP and autonomic nervous system. Due to the anatomy and constitution of the skull, cerebral circulation has a limited ability to expand, as it is difficult for this compartment to accommodate an increase in blood volume. CPP is one of the most important parameters for evaluating CBF. This can be easily calculated by subtracting the ICP value from the blood pressure value. It can be inferred that an increase in ICP without an increase in blood pressure leads to a reduction in the cerebral perfusion rate. This can be associated with the description of the 'Cushing's reflex', which refers to an increase in blood pressure, bradycardia and respiratory irregularities in response to an increase in ICP to pathological levels >25 mmHg (Cushing, 1901). In addition to these responses some studies suggest that physiological changes occur when ICP varies at lower levels (2–20 mmHg), and it is suggested that there is an intracranial reflex (Paton et al., 2009).

Studies carried out on sheep, rats and humans showed an increase in blood pressure in healthy animals when the ICP increased to physiological levels. In this case the hypothesis is that an increase in ICP levels is detected by astrocytes in the brain stem, promoting an increase in sympathetic nervous activity and consequently

contributing to a pressor response (Guild et al., 2018; Marina et al., 2020; Schmidt et al., 2018). Thus for increases in ICP within physiological parameters, the response occurs through the intracranial reflex, whereas for more significant increases, there is an activation of the Cushing's reflex.

These are ways of maintaining adequate cerebral perfusion without damaging the brain. It has even been proven that the inability to maintain normal levels is related to pathological situations such as vascular impairment, dementia and Alzheimer's disease (de la Torre, 2012). Previous studies have shown that hypertensive individuals have impaired cerebral perfusion compared with healthy individuals (Efimova et al., 2008; Vernooij et al., 2008; Warnert et al., 2016).

In 2021 Vari and colleagues showed that mild increases in ICP cause increased blood pressure mediated by the autonomic nervous system in awake sheep (Vari et al., 2021). However when the same experiments were performed with hypertensive sheep, the response was different, as the blood pressure response was attenuated. Furthermore data from our laboratory corroborate these findings, demonstrating the distinct neurophysiological mechanisms underlying hypertensive responses in rodent models. These results indicate elevated sympathetic reactivity in hypertensive states, suggesting that central modulation mechanisms may contribute to the exacerbation of autonomic dysfunction in response to ICP elevations (Vari et al., 2021).

Therefore it can be understood that an increase in ICP leads to a reduction in cerebral perfusion in hypertensive individuals because adjustment mechanisms are impaired. Hypertension is also related to impairing other mechanisms, such as the baroreflex and peripheral chemoreflex (Grassi et al., 1998; Somers et al., 1988; Trzebski et al., 1982).

Relationship between ICP, CSF and diurnal blood pressure changes. The relationship between ICP, CSF and diurnal blood pressure changes is complex and influenced by various factors. Under normal conditions ICP and CSF production exhibit diurnal variations. Research shows that ICP increases by ∼30% during the dark phase in both humans and rats, independent of vascular parameters (Steffensen et al., 2023). This increase corresponds with an elevated CSF collection in patients and CSF production rate in rats. The dark-phase increase in CSF secretion is partly attributed to increased transport activity of the choroid plexus Na+, K+, 2Cl– cotransporter (NKCC1) in rats (Steffensen et al., 2023).

Interestingly, the relationship between ICP, CSF and blood pressure patterns in hypertensive patients reveals some contradictions. Although ICP and CSF production increases during the dark phase, studies on hypertensive patients show that non-dippers (those who do not experience the normal nocturnal blood pressure dip) have higher uric acid levels and body mass index compared to dippers (Kanbay et al., 2011).

BBB dysfunction and ICP

BBB and hypertension. The BBB is a complex multicellular structure with the unique capability of restricting access to exogenous substances and blood-borne macromolecules in the CNS. Its primary function is maintaining homeostasis and providing an appropriate microenvironment for optimal neuronal activity. The core elements of the BBB comprise the endothelial cell layer, which contains tight junctions on their apical membrane, as well as pericyte and astrocyte end-feet. In addition a functional BBB comprises cells associated with the neurovascular unit (NVU), including neurons and microglia (Abbott et al., 2010; Ballabh et al., 2004; Sofroniew & Vinters, 2010). Under physiological conditions BBB permeability, selectivity and integrity are attributed to the collective composition and overall function of both the BBB and the NVU.

Central autonomic regulation homeostasis is also dependent on a functional BBB, as the BBB protects important anatomical regions of the brain, such as the medulla and hypothalamus, to sustain homeostasis in autonomic control centres (Smith & Ferguson, 2010). Whole-body homeostasis and blood pressure control are highly modulated by the periphery. Therefore circumventricular organs (CVOs), which are structures with specialized neuroepithelial cells, fenestrated capillaries and discontinuous tight junctions situated around the third and fourth ventricles, allow regular exchange between the brain and bloodstream (Ganong, 2000; Kiecker, 2018). CVOs play an essential role in regulating the release of hypothalamic hormones while detecting circulating concentrations of signalling peptides [e.g. angiotensin II (Ang II), ghrelin and leptin] and other signalling molecules capable of triggering autonomic modulation.

Among these signalling molecules Ang II is an important circulating peptide that regulates blood pressure, which does not cross the BBB unless this barrier is disrupted, as in chronic hypertension. Experimental studies have shown that acute and chronic hypertension can lead to BBB breakdown through various mechanisms (Biancardi & Stern, 2016; Candido et al., 2023; Mayhan et al., 1989; Perego et al., 2023; Ueno et al., 2004). Among these excessive or dysregulated Ang II signalling has been linked to BBB disruption in various experimental hypertensive conditions, including essential, Ang II-induced and renovascular-induced hypertension (Biancardi et al., 2014; Faraco et al., 2016). Specifically in spontaneously

hypertensive and renovascular hypertensive rats, BBB disruption occurs due to dysregulated Ang II signalling via Ang II type one receptor (AT1R). As a consequence of BBB disruption, circulating Ang II is allowed to act directly in critical cardiovascular nuclei within the hypothalamus and brainstem, including the paraventricular nucleus (PVN), rostral ventrolateral medulla (RVLM) and nucleus of the solitary tract (NTS) (Biancardi et al., 2014). Evidence of BBB breakdown due to Ang II is further supported by findings showing that Ang II-induced hypertension for 14 days promotes BBB disruption, whereas an acute Ang II infusion did not lead to the same effect (Faraco et al., 2016). Similar mechanisms have been observed in a mouse model of spontaneous hypertension (Faraco et al., 2016).

A number of mechanisms for Ang II leading to BBB dysfunction have been suggested. For instance in Ang II-induced hypertension for 14 days, circulating Ang II accesses the perivascular space, interacts with the perivascular macrophages and mediates responses through the activation of AT1R, ultimately resulting in NOX2-dependent reactive oxygen species (ROS) contributing to BBB dysfunction (Faraco et al., 2016). Additionally Santisteban et al. found that the activation of AT1R in endothelial cells of the arterioles that compose the BBB sets in motion the increased permeability of the BBB observed in Ang II-dependent and genetic models for hypertension (Santisteban et al., 2020). They further identified the conditional contribution of AT1R in perivascular macrophages to the BBB disruption via NADPH oxidase (NOX) 2 (Santisteban et al., 2020). Finally several studies have shown that AngII-AT1R dysregulation promotes the disruption of tight junctions, increases endothelial vesicle density and increases permeability via both paracellular and transcytosis transport (Candido et al., 2023; Fragas et al., 2021; Perego et al., 2023; Santisteban et al., 2020).

We recently demonstrated that Ang II and BBB disruption are closely associated with elevated ICP in renovascular hypertension (Fernandes et al., 2021). In our previous study we showed that administering the Ang II-AT1R blocker losartan to renovascular hypertension rats effectively prevented BBB disruption and partially restored blood pressure homeostasis (Fernandes et al., 2021). In contrast hydralazine, a direct vasodilator that lowers blood pressure without affecting Ang II-AT1R signalling, did not restore the integrity of the BBB. These effects of losartan were also accompanied by a robust ICP reduction, and most importantly, the ratio P2/P1 was also reversed to a normal condition, indicating an important improvement in ICC (Fernandes et al., 2021). Similarly hydralazine reduced blood pressure without altering ICP or ICC, further supporting the role of Ang II and BBB disruption in ICP regulation.

Neuroinflammation, BBB and ICP. Neuroinflammation is critical in the long-term dynamics of BBB permeability ICP. Besides the circulation of inflammatory factors and cells that can enter the CNS, another critical production of inflammatory molecules originates within the brain. Specifically these molecules are produced by glial cells of the NVU, namely astrocytes and microglia, which exacerbate BBB disruption and increase cerebrovascular permeability (Heneka et al., 2014; Sofroniew, 2015). Microglia, which are the inherent immune cells of the brain, are becoming more widely recognized for their involvement in hypertension. Specifically inhibition of microglial activity using minocycline in hypertensive rats reduced blood pressure, as demonstrated by Pelish and colleagues (Pelisch et al., 2011). Similarly the removal of microglia in transgenic mice has been shown to lower blood pressure and reduce the levels of tumor necrosis factor-α (TNF-α) and Interleukin-1 β (IL-1β) in the PVN of Ang II-hypertensive mice (Santisteban et al., 2015). These findings indicated that microglia play a role in the long-term maintenance of hypertension. In addition to microglia astrocytes can release various pro-inflammatory mediators, including TNF-α, IL-1β, monocyte chemoattractant protein-1 (MCP-1) and IL-6, when pathogens activate (Sofroniew, 2015). This allows further infiltration of immune cells and fluid into the brain parenchyma, contributing to vasogenic oedema and ICP elevation (Abbott et al., 2010; Sofroniew, 2015). Interestingly astrocytes can release vascular endothelial growth factors, which have been shown to disrupt the BBB and enhance the movement of white blood cells out of blood vessels (Argaw et al., 2012). Similarly oxidative stress-induced changes amplify BBB leakage, and disruption of its function has been shown in hypertension (Pires et al., 2013). ROS are the primary oxidative stress mediators that destroy the structure and function of proteins, DNA and lipids, thereby increasing the permeability of the BBB (Tan et al., 2004). This amplified production of free radicals results in a reduction in the expression of specific tight-junction proteins, thereby adversely affecting the BBB integrity (Witt et al., 2003). Nitric oxide (NO) is a signalling molecule that, among its multiple regulation roles, exerts a protective effect on the BBB by inhibiting amyloid plaque formation, tau phosphorylation and neuronal loss. However because this molecule is a free radical, its metabolite peroxynitrite has neurotoxic effects similar to ROS (Parathath et al., 2006). The release of ROS and nitric oxide from activated glial cells induces oxidative stress, damaging cerebral vasculature and impairing autoregulatory mechanisms. Over time chronic neuroinflammation can lead to maladaptive remodelling of cerebrovascular structures, reduced ICC and the perpetuation of elevated ICP. Therefore hypertension development depends on autonomic imbalance, RAAS, mechanical forces and chemical interactions

within the BBB. ICP will silently increase, and volume retention inside the cranium will persist. Indeed these positive feedback loops will continue, and new conditions for adaptation will be installed under robust organ damage. The cyclical interaction between inflammatory mediators, vascular dysfunction and ICP dynamics underscores the critical need for therapies targeting neuroinflammatory pathways to mitigate long-term cerebral damage and restore ICP homeostasis (Liddelow & Barres, 2017; Schwartz & Deczkowska, 2016).

BBB and cerebral venous pressure. BBB integrity is essential to maintaining CNS homeostasis and regulating ICP dynamics. In cases of acute, severe increases in arterial blood pressure, IH can occur, leading to increased BBB permeability by mechanisms associated with an increase in cerebral venous pressure, as previously demonstrated (Mayhan & Heistad, 1986; Mayhan et al., 1987). As a measure of the relation between pressure and flow, changes in arterial conductance are known for modifying perfusion so that increases in arterial pressure proportionally affect the flow and provoke a passive dilatation in blood vessels (Heistad & Marcus, 1979; Johansson et al., 1970; MacKenzie et al., 1976). This combination of simultaneous changes in these interdependent variables may disrupt BBB, and as a direct consequence, venous pressure may be affected not only by luminal fluid volume but also by changes in pressure exerted by parenchymal matter over vessels (Auer et al., 1980; Haggendal & Johansson, 1972). The study of Mayhan and Heistad examined whether veins and cerebral venous pressure contribute to the disruption of BBB and found that increases in venous pressure associated with acute arterial hypertension are enough to disrupt BBB, although fluid tonicity variations may also disrupt BBB in a venous pressure-independent manner (Mayhan & Heistad, 1986). This suggests that haemodynamic but not hydroelectrolytic components prominently contribute to BBB disruption in arterial and venous hypertension. Intriguingly subjects with chronic hypertension seem to exhibit a degree of protection against BBB disruption that relies on pial venular mechanisms capable of compensating for this haemodynamic-induced BBB damage. Undoubtedly further investigation is required to investigate the interdependent mechanisms linking the interrelation among BBB, venous and arterial pressure and its implications in ICP balance.

Elevations in cerebral venous pressure significantly impact BBB permeability through various mechanisms. At cerebral venous perfusion pressures exceeding 170 mmHg, significant alterations in BBB permeability are observed, especially within the superficial cortical layers, alongside a modest reduction in local cerebral blood flow (LCBF) (Ueda et al., 1989). These findings suggest a direct influence of elevated venous pressure on BBB integrity. Additionally venous congestion increases intracapillary pressure by obstructing capillary outflow and reducing blood flow velocity within capillary networks. This condition can result in an abnormally heightened permeability of the brain endothelium, potentially causing cerebral oedema and, in severe cases, petechial haemorrhages (Lockard, 1982).

Cerebral veins also exhibit a heightened sensitivity to blood flow variations associated with BBB opening compared to microvessels. Recent research utilizing advanced imaging techniques, such as laser speckle contrast imaging and wavelet analysis, has demonstrated that BBB disruption correlates with reduced venous CBF and increased complexity of venous circulation, whereas microvascular circulation remains unaffected mainly (Semyachkina-Glushkovskaya et al., 2017). These insights emphasize the critical role of cerebral venous pressure in modulating BBB permeability and underscore its broader implications for ICP dynamics, suggesting the need for further examination into venous contributions to cerebrovascular pathophysiology.

Choroid plexus and its associated blood–cerebrospinal fluid barrier and ICP

The choroid plexus and its associated blood–cerebrospinal fluid barrier (BCSFB) play a crucial role in maintaining ICP and are significantly affected by hypertension. The production of CSF is, in large part, carried out by the choroid plexus (Brinker et al., 2014). The choroid plexus is a highly vascularized structure located within the ventricles that contains fenestrated capillaries and specialized epithelial cells known as ependymal cells connected by tight junctions forming the BCSFB (Solar et al., 2020; Thompson et al., 2022; Yang & Shen, 2024).

Blood flow to the choroid plexus is significantly higher than that to the cerebral cortex, with a mean flow of 601 ml/100 g/min under basal conditions (Page et al., 1980). This high blood flow is essential for CSF production and maintenance of the barrier function. The importance of the choroid plexus–CSF barrier in ICP regulation is further highlighted in idiopathic intracranial hypertension (IIH). In this condition CSF and brain ISF hypersecretion occur simultaneously, leading to increased ICP (Iencean, 2003). The rapid circulation and absorption of these fluids, facilitated by maintained or increased CBF, help minimize brain injury despite the high ICP (Iencean, 2003). Additionally endogenous vasopressin release during hypoxia and increased ICP have a protective effect by constricting blood vessels in the choroid plexus, potentially reducing CSF production and helping to regulate ICP (Faraci et al., 1994). The blood–CSF barrier at the choroid plexus plays a crucial role in maintaining the delicate balance of CSF secretion, composition, volume and turnover (Bothwell

et al., 2019). Disruption of this balance can lead to increased ICP, which is implicated in various neurological conditions such as hydrocephalus, IIH, brain trauma, brain tumours and stroke (Bothwell et al., 2019; Tuta, 2022). Recent research suggests that pharmacological targeting of aquaporins, transiente receptor potential vanilloid 4 (TRPV4) and Na^+-K^+-Cl^- cotransporter 1 (NKCC1) may offer potential therapeutic avenues for managing impaired brain fluid dynamics and elevated ICP (Bothwell et al., 2019; Preston et al., 2018; Verkman et al., 2014). Indeed the role and involvement of these transporters in CSF secretion seem to affect ICP. For instance one study found that pharmacological inhibition of NKCC1 with bumetanide led to a reduction in ICP (Oernbo et al., 2022). In conclusion hypertension and inflammation can significantly impact the BBB and blood–CSF barrier, affecting CSF dynamics and ICP regulation. Understanding these mechanisms is crucial for developing effective treatments for neurological conditions associated with elevated ICP.

Chronic hypertension causes vascular remodelling, affecting the stroma, blood vessels and CSF production in the choroid plexus (Gonzalez-Marrero et al., 2022). González-Marrero et al. reported a distinct protein composition in the CSF of SHRs compared to normotensive wistar kyoto rats (WKYs) (Gonzalez-Marrero et al., 2013). These alterations are more pronounced in the BCSFB than in the BBB. Furthermore hypertension exacerbates age-related choroid plexus dysfunction, potentially contributing to neurodegenerative processes (Gonzalez-Marrero et al., 2022; Yang & Shen, 2024). Research indicates that acute hypertension can disrupt both the BBB and blood–CSF barrier, leading to increased permeability. In rabbits the threshold for BBB opening was ∼160 mmHg, whereas that for the blood–CSF barrier was 150 mmHg (Ziylan, 1984). This disruption is thought to be primarily due to the direct mechanical effect of increased intraluminal pressure in cerebral vessels, potentially causing the widening of tight junctions between endothelial cells (Ziylan, 1984). Interestingly chronic hypertension may have different effects on these barriers. A study using a novel magnetic resonance imaging technique found that SHRs exhibited a 36% reduction in blood–CSF barrier-mediated labelled arterial water delivery into ventricular CSF, indicating down-regulated choroid plexus function (Perera et al., 2022). This was accompanied by changes in brain fluid biomarkers, including ventriculomegaly and alterations in CSF composition.

In addition hypertension and increased BBB permeability have been observed in critical brain regions involved in the neurohumoral regulation of blood pressure, such as the paraventricular nucleus of the hypothalamus (PVN) and the RVLM (Biancardi et al., 2014). Interestingly the periventricular area, which is closely associated with the BCSFB, appears to be particularly vulnerable to disruption in conditions of inflammation and hypoxia. Severe hypoxia and high-dose lipopolysaccharide treatment resulted in prominent leakage in this area, suggesting blood–CSF barrier disruption (Nathoo et al., 2016). This finding highlights the importance of considering both the BBB and BCSFB when studying the effects of hypertension and inflammation on ICP regulation. The complex interplay between hypertension, inflammation and barrier disruption is complex and multifaceted. Both the BBB and BCSFB are affected, with potential implications for ICP regulation. Further research is needed to fully elucidate the mechanisms underlying these interactions and their impact on neurological conditions.

Brain drainage system, hypertension and ICP

The glymphatic system and meningeal lymphatic vessels have emerged as key players in the regulation of brain fluid dynamics, which are closely linked to ICP and cerebrovascular pathology. The glymphatic system facilitates the clearance of interstitial solutes, including metabolic waste, from the brain parenchyma via perivascular pathways, a process that is highly dependent on CSF circulation and arterial pulsatility (Iliff et al., 2012). Hypertension, particularly when it disrupts cerebral autoregulation, has been shown to impair glymphatic function by altering arterial compliance and reducing perivascular CSF influx (Mestre et al., 2018). These changes can exacerbate ICP dysregulation by diminishing waste clearance and contributing to ISF accumulation. Additionally meningeal lymphatic vessels, which drain the CSF and immune cells from the subarachnoid space into the cervical lymph nodes, may be implicated in the pathology of hypertension-induced ICP elevation. Hypertension has been associated with reduced meningeal lymphatic drainage, as evidenced by vessel remodelling and functional decline, leading to impaired CSF outflow and potential exacerbation of ICP. Dysregulation of these systems could also enhance neuroinflammatory responses, as impaired waste clearance and lymphatic drainage may allow the accumulation of pro-inflammatory cytokines and immune cells. Targeting the glymphatic and meningeal lymphatic systems, potentially through therapies aimed at enhancing CSF flow or reducing vascular stiffness, represents a promising avenue for mitigating ICP dysregulation and its neurological sequelae in hypertensive patients.

Conclusion

In conclusion hypertension significantly disrupts the intricate dynamics of ICP regulation and ICC, contributing to a cascade of severe cerebrovascular

and neurological consequences. This disruption is driven by a multifaceted interplay involving autonomic imbalance, the RAAS and the integrity of the BBB. Hypertension-induced changes in these systems lead to increased ICP, impaired cerebral perfusion and neuroinflammation, which collectively exacerbate the pathogenesis of cerebral ischaemia, neuroinflammation and cognitive decline. The BBB, a critical structure for maintaining cerebral homeostasis, becomes increasingly compromised under both acute and chronic hypertensive conditions. The NVU, comprising astrocytes, endothelial cells and microglia, plays a central role in these pathological processes, as hypertension-induced BBB permeability and neuroinflammation form a feedback loop that perpetuates ICP elevation and ICC impairment. Dysregulation of BBB integrity, due to an acute increase in blood pressure and the consequent increase in cerebral venous pressure, or chronically due to the exacerbation of RAAS activation and oxidative stress, leads to heightened permeability and infiltration of inflammatory mediators into the brain. This results in neuroinflammation and further exacerbation of ICP elevation. The glymphatic system and meningeal lymphatic vessels, critical for the clearance of metabolic waste and fluid balance, are also impaired under hypertensive conditions. Dysfunction of these clearance pathways contributes to waste accumulation and worsens ICP dysregulation, further highlighting the complexity of the interplay between hypertension, ICP dynamics and cerebral homeostasis.

Additionally factors such as cerebrovascular remodelling, alterations in CBV and CBF and changes in CSF dynamics add to the multifaceted mechanisms underlying ICP regulation in hypertensive states. The compromised BBB not only facilitates the entry of harmful substances into the brain but also disrupts the delicate balance of CBF, contributing to the loss of ICC. ICC, the brain's ability to accommodate changes in volume without significant increases in ICP, is crucial for protecting against cerebral damage. In hypertensive patients ICC is often impaired, reducing the brain's capacity to adapt to fluctuations in blood volume or CSF. This impairment leads to a loss of compensatory reserve, making the brain more vulnerable to damage from elevated ICP. As ICP continues to increase it creates a vicious cycle of further BBB disruption, neuroinflammation and oxidative stress, perpetuating the pathophysiological changes associated with hypertension. Moreover hypertension-induced alterations in the autonomic nervous system, particularly the SNS, further contribute to the destabilization of ICP and ICC. The SNS plays a crucial role in regulating CBF and maintaining normal ICP levels. However in hypertensive conditions this regulatory mechanism becomes impaired, leading to increased cerebral ischaemia risk and other complications. This ongoing positive feedback loop between hypertension, BBB disruption and ICP elevation highlights the urgent need for early detection and intervention.

Understanding these mechanisms offers critical insights into the pathophysiology of hypertension-related brain dysfunction. Interventions aimed at preserving BBB integrity, reducing neuroinflammation and improving ICC could mitigate the devastating consequences of uncontrolled hypertension on cerebral health. Advances in ICP monitoring, non-invasive measurement techniques and targeted therapies for enhancing glymphatic and meningeal lymphatic clearance pathways hold promise for improving outcomes in hypertensive patients at risk for cerebrovascular disorders, cognitive impairment, and stroke. Without timely management these conditions can lead to significant brain damage, cognitive decline and an increased risk of stroke and other cerebrovascular events. Effective strategies to mitigate the impact of hypertension on cerebral health must focus on preserving BBB integrity, reducing neuroinflammation and improving ICC. By addressing these underlying mechanisms, it may be possible to break the cycle of damage and prevent the progression of brain dysfunction in hypertensive patients. Future research and clinical interventions should prioritize these areas to reduce the burden of hypertension-related brain disorders and improve patient outcomes.

This review emphasizes the need for early detection and timely intervention to protect brain health in hypertensive individuals. Future research should focus on identifying novel therapeutic targets and optimizing clinical management strategies to address the complex interplay between systemic hypertension and ICP regulation, ultimately improving neurological outcomes and reducing the burden of hypertension-related brain disorders.

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Additional information

Competing interests

No competing interests declared.

Author contributions

E.C.: conception or design of the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work. V.C.B.: conception or design of the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work. D.S.A.C.: conception or design of the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work. P.L.K.: conception or design of the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work. F.C.M.: conception or design of the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work. A.V.A.: conception or design of the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work. C.H.X.: conception or design of the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work. G.R.P.: conception or design of the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work. D.E.B.: conception or design of the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

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