Intracranial Pressure and Collateral Blood Flow

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Leptomeningeal collateral vessels, linking the 3 major arterial territories over the surface of the brain, have been recognized for >140 years. More widespread use of advanced clinical imaging in the past decade has led to increasing recognition of the key importance of collaterals in ischemic stroke outcome. However, recent studies from several groups indicate that failure of initially good collateral supply is a key feature of patients with delayed infarct expansion. This clinically challenging problem typically occurs in the first 1 to 2 days after hospital admission in patients with initially mild stroke symptoms. Rethrombosis of reperfused vessels was previously thought to be the likely cause of delayed infarct expansion in most patients. However, this theory is not supported by more recent evidence from imaging studies. Despite the important recent observations, there is limited understanding of the dynamic control of the collateral circulation, in particular, the cause of collateral blood flow failure. In this article, we will discuss recent observations from our experimental stroke model, indicating a dramatic increase in intracranial pressure (ICP) occurring around 24 hours after onset of even small stroke. We have also shown a significant linear reduction of collateral blood flow in response to progressive ICP elevation. We believe that a similar transient ICP elevation occurring during the first 1 to 2 days post stroke is a likely mechanism to explain delayed infarct expansion in patients with minor stroke. Perhaps surprisingly, we can find no published data on ICP at 24 hours in patients with minor stroke. The preclinical findings suggest that gathering such data should be a priority.

Collaterals and Stroke Outcome

Human Stroke

There is a strong association between the extent of leptomeningeal collaterals and clinical stroke outcome. Initial studies using digital subtraction angiography permitted direct visualization of collateral vessels and the time taken for retrograde contrast filling of the ischemic territory. The advent of dynamic computed tomography angiography and magnetic resonance contrast angiography has permitted noninvasive assessment of the presence/extent of retrograde contrast filling of the occluded arterial tree. Good flow through leptomeningeal collaterals, most commonly from anterior cerebral artery (ACA) or posterior cerebral artery territories to the middle cerebral artery (MCA) territory is associated with smaller baseline infarcts, larger baseline penumbra, reduced incorporation of the penumbra into the infarct core, smaller final infarct volume, and better long-term outcomes. For those seeking more detail, several comprehensive reviews of the importance of collateral circulation and its potential as a therapeutic target for stroke are available.

Experimental Stroke

The collateral circulation in the rodent strains commonly used to model stroke is closely analogous to that of humans, including significant variability in both number and diameter of leptomeningeal collaterals (both between and within animal strains). As in patients, there is a strong association between good collateral supply and good stroke outcome. These findings have been consistent in experiments in which collateral supply was quantified postmortem (number and diameter of vessels) or using functional measurement of tissue perfusion within the watershed region between the ACA and MCA. A distinct advantage of animal studies is that thinning or removal of the skull is possible, and this has allowed direct visualization of leptomeningeal collaterals in vivo. These studies suggest that collaterals may have dual roles. First, they act as a primary vascular network, perfusing the watershed penetrating arterioles between the MCA and the ACA during normal conditions. The penetrating arteriole at the midpoint of each collateral vessel receives blood supply from the 2 vascular territories they connect. The penetrating arteriole at the point where the opposing flows meet can be seen to receive fluorescently labeled microspheres or blood cells from both. Interestingly, perfusion to these watershed penetrating arterioles seems to be maintained after stroke onset, despite major changes in blood flow direction and velocity within the feeding collateral vessel.

Second, collaterals represent a subsidiary vascular network able to provide retrograde perfusion to the ischemic territory during major vessel occlusion. Collateral blood flow changes from bidirectional to unidirectional, toward the occluded arterial territory (MCA), and increases in velocity. The degree of retrograde flow is proportional to regional cerebral blood flow within the MCA territory. In
other words, the leptomeningeal collateral vessels are the major factor affecting residual perfusion of the ischemic penumbra during ischemic stroke. Collateral vessels are uniquely suited to this role because they have much greater baseline diameter than that of other parts of the arterial tree with similar flow rates.22 This large diameter means that if the pressure differential across the collateral vessel increases, as occurs during occlusion of 1 arterial territory, there is an immediate and dramatic increase in blood flow.7 This is explained by the strong dependence of flow on vessel diameter (flow proportional to the fourth power of the radius).23 Interestingly, in our work, we saw little change in collateral vessel diameter in the first 2 hours after stroke onset, despite dramatic increases in blood flow.7 This suggests that strategies that enhance the pressure differential across collateral vessels (eg, cerebral perfusion pressure [CPP] elevation) may be the most fruitful approach to manipulate collateral flow therapeutically. Conversely, it suggests that anything that reduces this pressure differential (eg, hypotension or ICP elevation) may be detrimental to collateral perfusion, with clear potential clinical implications.

Collateral Vessels and Delayed Infarct Expansion

The term stroke-in-progression is currently used to describe patients with stroke who deteriorate after admission to hospital, regardless of underlying pathophysiology.24 It occurs in ≈10% to 40% of patients with stroke.25 However, recent more widespread use of sequential noninvasive angiography and perfusion imaging has resulted in the identification of patients who have delayed infarct expansion within the initially ischemic arterial territory as the cause of their neurological deterioration, as opposed to edema, or new infarction in a different arterial territory.3,4 Those patients with delayed infarct expansion typically have mild or rapidly improving symptoms at the time of hospital presentation, and most commonly deteriorate during the first full day in hospital after admission.26 They are not normally treated with reperfusion therapies because their symptoms are considered too mild when assessed acutely (National Institutes of Health Stroke Scale <5).27 They are also normally ineligible for reperfusion therapies when they deteriorate because of the excessive bleeding risk at such late time intervals from stroke onset, whether using lytic agents or endovascular clot retrieval.5,28 Despite typically presenting with mild symptoms, most of these patients leave hospital worse than when they arrived; >50% require assistance with daily tasks at 3 months.29 This is a source of great angst to patients, families, and treating clinicians.

Collateral Failure Is Associated With Delayed Infarct Progression

Until recently, the pathophysiology assumed to explain clinical improvement then subsequent deterioration was the presence of spontaneous vessel recanalization followed by rethrombosis of the initially occluded artery. However, recent advanced imaging studies from several groups indicate that the arterial occlusion does not change between acute and follow-up imaging.3,4,29 What does change is collateral supply. Leptomeningeal collateral supply is typically good at the time of acute imaging, but deteriorates by the time of follow-up imaging (collateral failure).4 We suggest that such patients most likely do reperfuse to some extent in the acute phase, in the form of good retrograde perfusion to the ischemic penumbra via collateral vessels (reperfusion without recanalization). This may account for the early clinical improvement seen in many. The key unanswered question is why an initially adequate collateral blood supply should decline over time? Many possible mechanisms have been proposed. These include collateral vessel thrombosis, venous steal, Reversed Robin Hood syndrome, and blood pressure fluctuations secondary to autonomic dysfunction.30–33 However, there is little direct evidence and no consensus on the cause for collateral failure.

CPP and Collaterals

The idea that therapeutic alterations in CPP can alter perfusion of the ischemic penumbra via collaterals is long-established but until recently had not been directly tested.34 The CPP is the difference between mean arterial pressure and ICP (CPP=mean arterial pressure−ICP).35 Under normal physiological conditions, deviations in cerebral blood flow are minimized by autoregulation. However, during stroke, autoregulation is lost, so perfusion to the ischemic penumbra via leptomeningeal collateral vessels is thought to be CPP dependent.34 Studies in animal models of stroke have successfully demonstrated a relative increase in blood flow in the distal ACA and ACA–MCA leptomeningeal collaterals by increasing CPP using pharmacological pressor therapy (eg, phenylephrine) or partial aortic occlusion.21,36 Many small clinical studies have also attempted to enhance perfusion to the penumbra using pressor therapy, partial aortic occlusion, or external counterpulsation.37–39 However, the efficacy of these approaches in terms of improving penumbral perfusion and clinical outcomes is yet to be demonstrated in large randomized trials. Much less attention has been paid to the other side of the CPP equation, ICP. Because of the effect on CPP, an increase in ICP post stroke may also reduce collateral blood flow by reducing the driving pressure of flow across collateral vessels. Therefore, ICP elevation is a possible mechanism for collateral failure in stroke-in-progression.

ICP Elevation After Stroke: Importance for Collateral Blood Flow

Monroe40 and Kellie41 first enunciated the ideas that govern our understanding of ICP regulation, well over a century ago. In summary, the Monroe–Kellie doctrine states that the intracranial compartment is a closed system within the non-expandable, rigid skull and is made up of 3 noncompressible elements that determine ICP: tissue, blood, and cerebrospinal fluid (CSF). The cranium has little capacity to accommodate any additional volume. To maintain normal ICP, any increase in the volume of 1 intracranial compartment must be compensated for by a subsequent reduction in the volume of the other compartments. Once these compensatory mechanisms are exhausted, any additional increase in volume results in large increases in ICP. Elevated ICP is a significant problem in several forms of neurological injury including stroke.42,43
subarachnoid hemorrhage, traumatic brain injury, and intracerebral hemorrhage and can lead to secondary neurological injury and sometimes death.

**ICP Elevation After Stroke**

ICP elevation is known to occur between 1 and 3 days after large hemispheric ischemic stroke and dramatic ICP rise is frequently a preterminal event. However, we have no information about ICP in patients fitting the profile of those who develop delayed infarct expansion because ICP is not normally monitored in those with (initially) mild stroke, because of the invasive nature of ICP monitoring. Recent experimental evidence suggests that there is a previously unrecognized, dramatic ICP elevation after even minor ischemic stroke, lasting for many hours, with its peak ≈24 hours post stroke onset (Figure 1). Previous studies did not specifically investigate mild stroke, but also suggested an early ICP peak with similar timing. Silasi et al found a peak in ICP at ≈24 hours in rats with moderate to large strokes. Kotwica et al produced variable sized ischemic strokes and found that both small and large strokes had an ICP peak at 24 hours; however, the larger strokes went onto have a second peak at 3 days. Recently, our laboratory have demonstrated 24-hour ICP elevation, occurring in 3 different rat strains (Wistar, Long Evans, and Sprague–Dawley) and 2 different stroke models (proximal intraluminal MCA occlusion and small cortical photodisruption stroke), in both young and aged animals (L.A. Murtha, PhD, unpublished data). Interestingly, the early (24 hours) ICP elevation is not caused by edema. ICP elevation >30 mm Hg was seen even in animals with tiny infarcts and volumes of edema. The lack of a link to edema volume was a consistent finding in several series of experiments using histology, wet-dry weight, or in vivo magnetic resonance imaging to measure edema. This then raises the question of why ICP should rise? Using the Monroe–Kellie principles as a conceptual framework, we suggest that either blood volume or CSF volume increases are the likely cause. Our preliminary data implicate the latter. An increase in CSF volume can either be because of an increase in CSF production or a reduction in CSF outflow. However, the exact mechanisms and locations of CSF production and outflow under physiological conditions are still controversial. Therefore, additional studies are clearly required to better understand CSF dynamics under normal conditions and after neurological injury. Irrespective of the mechanism, the presence of a similar ICP rise and accompanying reduction in CPP in patients would have important implications for stroke outcome.

**ICP and Collateral Blood Flow**

We recently obtained experimental confirmation of the hypothesis that ICP elevation reduces collateral flow post stroke. We were able to accurately quantify individual collateral vessel flow during artificial ICP elevation in animals with experimental MCA occlusion. ICP was raised in a stepwise manner to 30 mm Hg, replicating the median rise seen 24 hours post stroke in our models. There was a linear reduction in collateral flow with increasing ICP, to a mean 55% reduction in leptomeningeal collateral blood flow at 30 mm Hg (Figure 2). Such a reduction to the already tenuous penumbral perfusion would be expected to have major effects on penumbral survival. Interestingly, ICP elevation caused little change to collateral vessel diameter but caused a profound reduction in blood flow velocity, as would be predicted by effects of reduction of CPP on the driving pressure for flow across the collateral vessel. Blood pressure remained stable, and blood flow was closely correlated with CPP.

In those studies in which it has been measured, ICP elevation at 24 hours seems to be a ubiquitous finding in rats, but has only recently been remarked on, despite the fact that likely hundreds of thousands of animals have been studied using these models of experimental stroke. Proof of a similar ICP elevation in patients with small stroke has not yet been obtained. However, most other major pathophysiological mechanisms are largely preserved across mammalian species, and we think that this is likely to be the case for the observed ICP response too.

**Therapeutic Hypothermia Is a Potential Clinical Therapy for Preventing ICP Elevation**

Therapeutic hypothermia has been a focus of neuroprotective research in stroke and other disorders for many decades. It
has probably the strongest weight of evidence of any neuroprotective strategy studied in experimental stroke models. There is also a randomized trial evidence of benefit in human brain ischemia after cardiac arrest and neonatal hypoxia ischemia. Hypothermia has been shown to decrease elevated ICP in several neurological disorders, including several phase II stroke clinical trials. These studies used long durations of cooling (24–72 hours) and often encountered problems of systemic infection and rebound ICP elevation during patient rewarming. In stark contrast to the paradigm used clinically, the strong evidence of neuroprotection in animal models of stroke comes overwhelmingly from studies using short-duration hypothermia.

Furthermore, recent studies in our laboratory have demonstrated that short-duration hypothermia, administered 1 hour after onset, completely prevented the dramatic 24-hour ICP rise that was seen in noncooled animals (Figure 1). This raises the possibility that at least some of the observed benefit in the experimental literature could be because of the previously unrecognized effect of the short-duration hypothermia preventing intracranial hypertension. Previously, it has been assumed that most of the benefits of hypothermia were from slowing metabolism in ischemic tissues and prevention of edema. Work from our group and collaborators indicates that the edema-preventing effect of short-duration hypothermia are relatively modest, even in animals with moderate-sized stroke; however, the prevention of ICP elevation is absolute. ICP is ≈4-fold higher in stroke animals maintained in normothermia than in those treated with short-duration hypothermia. The ICP rise is consistently prevented by moderate hypothermia (to 32.5°C for 2.5 hours, commencing 1 hour post stroke). However, promisingly in terms of potential future clinical translation, mild hypothermia (35°C) seems equally beneficial for ICP prevention. In the clinical setting, short-duration hypothermia would be safer, easier to implement, and potentially more widely applicable than long-duration hypothermia. Increasingly widespread use of advanced imaging for acute stroke may allow identification of the subset of patients at highest risk of delayed infarct expansion. Short-duration hypothermia is a potential treatment approach that could be tested in future imaging-selection trials.

Conclusions

Our own data and that of previous investigators indicate that ICP rises dramatically ≈24 hours after experimental stroke. Countering previous assumptions, edema does not seem to be responsible for this pressure rise. Proof of the exact mechanism is not yet available, but an increase in CSF volume is hypothesized. At much the same time as we made the observations of ICP rise, several groups were reporting evidence of a likely new mechanism for delayed infarct progression in patients with stroke. The previously widespread assumption that recurrence or extension of thrombosis was the common cause was not supported by the imaging data. Rather, it suggested that failure of collateral vessels played an important role. We now have animal imaging data showing that ICP elevation reduces blood flow through collateral vessels during stroke. The similar timing of ICP elevation in the experimental animals and infarct expansion in patients suggests that ICP elevation may be the explanation for collateral failure. However, there are clearly still a multitude of unanswered questions. Our hope is to encourage further discussion among basic scientists and clinicians interested in stroke, to provide answers and new therapies for the clinically devastating (and professionally challenging) problem of delayed infarct expansion.

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Disclosures

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