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Cerebral Autoregulation and Acute Ischemic Stroke

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Cerebral autoregulation tightly controls blood flow to the brain by coupling cerebral metabolic demand to cerebral perfusion. In the setting of acute brain injury, such as that caused by ischemic stroke, the continued precise control of cerebral blood flow (CBF) is vital to prevent further injury. Chronic as well as acute elevations in blood pressure are frequently associated with stroke, therefore, understanding the physiological response of the brain to the treatment of hypertension is clinically important. Physiological data obtained in patients with acute ischemic stroke provide no clear evidence that there are alterations in the intrinsic autoregulatory capacity of cerebral blood vessels, except perhaps in infarcted tissue. While it is likely safe to modestly reduce blood pressure by 10–15 mm Hg in most patients with acute ischemic stroke, to date, there are no controlled trial data to indicate that reducing blood pressure is beneficial. There may be subgroups, such as those with persistent large vessel occlusion, large infarcts with edema causing increased intracranial pressure or local mass effect, or chronic hypertension, in which blood pressure reduction may lead to impaired cerebral perfusion in noninfarcted tissue.

Keywords: *blood pressure; cerebral autoregulation; hypertension; ischemic stroke*

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Under normal physiological conditions, cerebral blood flow (CBF) is matched to the metabolic demands of the brain preventing cerebral ischemia. This process is accomplished via several structural as well as adaptive features of the cerebral circulation including autoregulation. Cerebral autoregulation refers to the complex multifactorial process that maintains blood flow to the brain as the systemic blood pressure and hence cerebral perfusion pressure changes over a wide range. If cerebral autoregulation is impaired the brain becomes more vulnerable to ischemic damage caused by changes in systemic blood pressure or intracranial pressure. This impairment could affect the efficacy and safety of treatment algorithms in the setting of acute hypertension and ischemic stroke. In the absence of definitive data from clinical trials showing that any treatment affects outcome, the best clinical practice for the management of blood pressure, whether hypotension or hypertension, in the setting of ischemic stroke is unclear.[1,2] The published literature on cerebral autoregulation in the setting of ischemic stroke is inconclusive and its interpretation is subject to several limitations. This article will discuss the results of studies evaluating cerebral autoregulation in patients with acute ischemic stroke and how it may apply to the clinical setting.

CEREBRAL AUTOREGULATION OVERVIEW

Cerebral autoregulation enables the brain to match its metabolic demand to the supply of blood both regionally as well as globally. Both animal and human studies have clearly demonstrated that CBF remains relatively constant within a fixed range even in the setting of significant fluctuations in mean arterial pressure (MAP) and resultant changes in cerebral perfusion pressure.[3] Human studies have shown that in normotensive individuals the limits of autoregulation for which CBF remains relatively constant are from a MAP of 60–150 mm Hg.[3,4] When the MAP is within these limits, the blood flow is actively controlled by reciprocal changes in arterial tone to meet the demands of the brain; however, below or above this range, the autoregulatory capability of cerebral arteries is compromised and the CBF becomes a more passive process.

When the MAP is not within the limits of autoregulation, there is a risk of brain injury from unregulated CBF. If the MAP decreases to a level below the lower limit of autoregulation, the CBF may decrease such that it no longer meets the metabolic demands of the brain. At this point, the vessels are maximally dilated in an attempt to reduce the vascular resistance and increase flow. Once blood flow falls below a critical threshold, cerebral ischemia ensues which can lead to irreversible loss of brain tissue, ischemic stroke. At the other end of the spectrum, if the MAP is above the upper limit of autoregulation, the cerebral blood vessels are no longer able to adequately constrict in an attempt to limit blood flow. The loss of autoregulation results in blood flow becoming passive leading to endothelial injury and breakdown of the blood–brain barrier with resultant cerebral edema. Clinical studies have also demonstrated that the autoregulatory curve can be affected by chronic hypertension with an upward shift in both the lower and upper MAP thresholds.[5] Clinically, this may become important in the setting of acute ischemic stroke. Reducing the

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blood pressure too aggressively in these circumstances could potentially lead to cerebral hypoperfusion at a MAP that is within the "normal" autoregulatory limits.

While true autoregulatory failure occurs when there is an impaired blood vessel response when the perfusion pressure is within the autoregulatory range, a "falsely" impaired autoregulation may also be seen. If the local cerebral perfusion pressure is below the autoregulatory range while the MAP is not, it may appear that there is impaired cerebral autoregulation. This can occur with elevated intracranial pressure, venous obstruction, locally from the mass effect of cerebral edema or a mass lesion or persistent arterial occlusion. If the artery remains occluded, the downstream perfusion pressure in that vessel will be reduced and may be below the lower autoregulatory limit. Under these circumstances, regional CBF may decrease with reduction in systemic blood pressure but it is not because the autoregulatory capacity of the vessels is damaged by the ischemia, but simply because their normal vasodilatory capacity is exhausted. This may explain the findings in animal models of stroke with permanent vessel occlusion.[6]

Furthermore, the measured autoregulatory response may be confounded by the concurrent treatment of hypertension with antihypertensive agents such as alpha-blockers and cerebral blood vessel dilators. These agents may impair the ability of the cerebral blood vessels to dilate or constrict as necessary to regulate blood flow.[7–10]

Whether autoregulation is truly or falsely impaired, both circumstances could be clinically important as a reduction in MAP or increase in intracranial pressure could lead to a significant reduction in local CBF. This is especially true if the CBF is already reduced to the point at which oxygen supply is close to the level of oxygen demand. Under these circumstances even small reductions in MAP could result in a decrease in CBF below the critical threshold leading to cerebral ischemia and, if persistent and low enough, cerebral infarction.

CEREBRAL AUTOREGULATION IN ACUTE ISCHEMIC STROKE

The integrity of cerebral autoregulation in the setting of acute ischemic stroke is of significant clinical importance. Ischemic stroke occurs as the result of a decrease in the blood flow below a critical threshold to an area of the brain leading to neuronal death. Many have postulated that this initial ischemia in itself may lead to dysfunctional autoregulation in the surrounding regions or even in some cases both hemispheres.[11–17] If autoregulation were to be impaired, further areas of brain would be at risk for ischemia that could be confounded by aggressive blood pressure reduction. Clinically this is important because transient hypertension is seen in >60% of patients after ischemic stroke and its proper treatment remains unclear.[18–22]

Ischemic stroke by definition is the death of brain tissue that is caused by hypoperfusion below a critical threshold for a prolonged period of time. While the core of the infarction is irreversibly damaged, there may be a penumbra of tissue that is surrounding the core in which the hypoperfusion is not low enough or for long enough to have caused infarction, yet it is at risk for infarction if the hypoperfusion persists or worsens. The penumbra is the tissue at which most clinical treatments are aimed at salvaging.

While there have been numerous studies directed at better understanding cerebral autoregulation in the setting of ischemic stroke, the conclusions drawn from them have been inconsistent, thus their clinical applicability has been unclear. The earliest studies, prior to the advent of cerebral imaging modalities such as computed tomography, positron emission tomography (PET), and magnetic resonance imaging, used the technique of radioisotope injection into the carotid artery with measurement of radioactivity over the brain area of interest using scintillation crystals on the scalp.[23–26] While this technique allowed for the determination of quantitative regional CBF, it was not possible to differentiate core from penumbra from nonischemic tissue. While these studies did demonstrate focal abnormalities in autoregulation of the affected hemisphere, it is not clear in what type of tissue the abnormalities occurred.[27]

A series of more recent studies have examined cerebral autoregulation in the context of ischemic stroke during the treatment of the associated hypertension using other techniques. Nazir *et al.* conducted a pair of studies in patients with acute ischemic stroke evaluating the effect of two different antihypertensive agents on cerebral autoregulation.[28,29] In the first study, 24 patients with a recent ischemic stroke or transient ischemic attack were randomized to receive either placebo or oral losartan. While the MAP decreased by 9.1 mm Hg at 1–12 h postdose in the losartan group, there was neither a change in CBF measurement by single-photon emission computed tomography nor any change in internal carotid artery flow as measured by transcranial Doppler. In the second study, Nazir *et al.* evaluated 25 patients within 4–8 days of an ischemic stroke or transient ischemic attack to determine whether lowering blood pressure with perindopril would affect cerebral perfusion.[29] Although those randomized to the antihypertensive agent had a mean MAP reduction of 9.3 mm Hg, no significant change was seen in internal carotid artery flow or middle cerebral artery blood velocity as measured with transcranial Doppler or CBF as measured by single-photon emission computed tomography. Rashid *et al.* have shown that patients randomized within 72 h of ischemic stroke to receive transdermal nitrate as compared to controls had no difference in CBF velocity in the affected hemisphere even though the MAP was significantly reduced.[30]

In patients with large ischemic strokes, such as malignant middle cerebral artery infarcts, cerebral autoregulation to small

spontaneous fluctuations in blood pressure has been shown by transcranial Doppler to be significantly altered.[31,32] These studies each demonstrated that for patients with impaired cerebral autoregulation in the ipsilateral hemisphere to the stroke, the clinical outcome was worse when compared to those with intact autoregulation.

There are some limiting factors in utilizing transcranial Doppler to evaluate cerebral autoregulation. The measurement is made via insonation of the middle cerebral artery or internal carotid artery that supplies a large portion of the cerebral hemisphere. One is relying on a relatively global value while the strokes are affecting various proportions of the territory perfused by the large artery. The sensitivity of this measurement is likely to be directly affected by the amount of tissue affected by the stroke. For small strokes this measurement may be too insensitive to identify changes in autoregulation while in large hemispheric strokes affecting the majority of the middle cerebral artery territory, one may be solely evaluating the autoregulation of the core infarct. It is not possible to distinguish the surrounding penumbra from the core.

Other studies have been performed with tomographic techniques that offer superior spatial resolution. Pozzilli *et al.* evaluated seven patients within 6 h of onset of symptoms of stroke.[33] Regional CBF was measured using single-photon emission computed tomography and CBF analysis was performed before and repeated 30 min after intravenous nimodipine was administered. While the MAP was lowered from 111 ± 15 to 97 ± 13 mm Hg there was no reported change in core infarct or contralateral hemispheric CBF; however, there was an increase in the CBF in the peri-infarct tissue.

Cerebral autoregulation in the setting of acute ischemic stroke has additionally been studied with PET. Some of the benefits of PET compared to other modalities are that PET is high resolution, accurate quantitation, and allowance for the identification of the infarct and peri-infarct regions. Hakim *et al.* randomized 14 patients to either intravenous nimodipine or carrier solution within 48 h of acute stroke.[17] PET scans were performed at the time of randomization and at 7 days. CBF measurements did not demonstrate impairment in cerebral autoregulation in the peri-infarct region of the brain even with a 10-15 mm Hg reduction in systolic blood pressure (SBP). Powers *et al.* evaluated the effect of acute and rapid blood pressure reduction on the CBF in seven patients after acute ischemic stroke.[34] Although MAP was decreased by a mean of 16 mm Hg over a mean of 63 min, there was not selective regional impairment in CBF autoregulation in the core, penumbra or remainder of the affected hemisphere. In this study, two individuals had global reductions of hemispheric CBF with MAP reductions. The findings in these two participants were consistent with a shift upwards in the whole brain autoregulatory curve due to chronic hypertension. One of these two patients developed transient worsening of his focal neurological deficit during blood pressure reduction. When MAP is reduced below the lower limit of autoregulation, CBF will decrease uniformly in the whole brain. In the setting of acute ischemic stroke, neurons in the penumbra area with CBF values just above the threshold for normal neuronal function will be the first to become dysfunctional as CBF decreases globally. Thus, although the CBF reduction is uniformly global, the symptoms may be a focal worsening of the existing neurological deficit.

Based on the available data we conclude that there is no clear evidence that there are alterations in the intrinsic autoregulatory capacity of cerebral blood vessels in acute ischemic stroke, except perhaps in infarcted tissue. The clinical studies with adequate spatial resolution haven't shown selective decreases in CBF with reductions in MAP in the infarct or penumbra area. These studies were not designed to address the effects of MAP reduction in patient with persistent arterial occlusion or large infarcts with edema causing local increases in intracranial pressure, both of which can lead to apparent ("false") autoregulatory impairment due to local reductions in cerebral perfusion pressure below the autoregulatory limit. In these circumstances and in patients with chronic hypertension, reduction of MAP even within the normal autoregulatory range, could lead to local hypoperfusion and ischemia in noninfarcted tissue. These data deal only with physiological measurements and not with patient outcomes. For those, we need to turn to randomized clinical trials.

These conclusions are based on studies of static autoregulation in which the blood pressure was lowered over minutes or longer and there was sufficient spatial resolution to differentiate infarcted from noninfarcted tissue. Another technique to investigate the response of CBF to changes in blood pressure employs the correlation between changes in blood vessel flow or volume to spontaneous fluctuations in arterial or intracranial pressure that occur over seconds ("dynamic autoregulation"). While this dynamic autoregulation may be impaired in the setting of unimpaired static autoregulation, the clinical relevance of these measurements is unclear.[35]

CLINICAL TRIALS OF HYPERTENSIVE MANAGEMENT IN ACUTE STROKE

Three randomized clinical trials evaluating the treatment of hypertension in the setting of acute stroke have been reported. The Controlling Hypertension and Hypotension Immediately Post-Stroke (CHHIPS) trial randomized 179 patients with acute ischemic or hemorrhagic stroke whom also had a SBP >160 mm Hg, to either oral labetalol, lisinopril or placebo within 36 h of onset.[36] While the antihypertensive agents were effective in lowering SBP by a mean of 21 mm Hg in the intervention group vs. 11 mm Hg in the control group, there was no

significant effect on clinical outcome. The major limiting factor for this study was the small sample size. The Scandinavian Candesartan Acute Stroke Trial (SCAST) reported this past year was also a randomized, placebo-controlled, double-blind trial however it was much larger enrolling 2,029 patients with acute stroke.[37] Of the enrolled patients, 85% had an acute ischemic stroke and 14% a hemorrhagic stroke, all of which had an associated SBP >140 mm Hg. Patients were randomly assigned to treatment with candesartan or placebo and the outcomes measured were two coprimary effect variables: the composite endpoint of vascular death, myocardial infarction, or stroke during the first 6 months; and functional outcome as measured by the Modified Rankin scale at 6 months. As with the CHHIPS trial, BP was significantly lower in the treatment group, 147/82 for the treatment group vs. 152/84 for the placebo group, however there was no significant primary outcome benefit. Based on these and other data, there does not appear to be a significant benefit or detriment to acute blood pressure reduction in acute ischemic stroke. The COSSACS trial was aimed a determining the safety and efficacy of stopping vs. continuing pre-existing antihypertensive agents for those with acute ischemic stroke.[38] At the time of admission, 763 patients were randomized to continue or stop taking their pre-existing antihypertensive medications for two weeks. The primary outcome was death or dependency at 2 weeks. While those patients in whom their anti-hypertensive agents were discontinued had a significantly higher blood pressure, SBP 13 mm Hg and diastolic blood pressure 8 mm Hg higher compared to those that continued antihypertensive medications, there was no significant difference in primary outcome. Furthermore, there was no difference in the rates of serious adverse events, 6-month mortality, or major cardiovascular events.

CURRENT GUIDELINES

Current guidelines for the management of blood pressure elevation in the setting of acute ischemic stroke were derived before the publication of these three clinical trials. They are based on expert opinion, retrospective analyses, and small trials, as at the time no higher level of evidence was available.[2,39] These guidelines recommend blood pressure reduction for severe elevation in blood pressure or if there is evidence for other end-organ damage such as myocardial ischemia or encephalopathy.[1,2] The treatment threshold is for a SBP >180 mm Hg unless reperfusion therapy has been utilized. The SCAST trial provided a subgroup analysis based on baseline blood pressure and reported no benefit in those whose initial blood pressure was >180 mm Hg.[37] If intravenous rtPA has been administered the treatment threshold is a SBP >180 mm Hg or diastolic blood pressure >105 mm Hg to reduce the risk of hemorrhagic transformation. This recommendation is based on the protocols of the intravenous rtPA trials.[40–42]

CONCLUSION

Physiological data obtained in patients with acute ischemic stroke provide no clear evidence that there are alterations in the intrinsic autoregulatory capacity of cerebral blood vessels. While it is likely safe to modestly reduce blood pressure by 10–15 mm Hg in most patients with acute ischemic stroke, to date there are no controlled trial data to indicate that reducing blood pressure is beneficial. There may be subgroups, such as those with persistent large vessel occlusion, large infarcts or chronic hypertension, in which blood pressure reduction may lead to impaired cerebral perfusion.

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