Neurocritical care and periprocedural blood pressure management in acute stroke

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ABSTRACT

The purpose of this article is to review the literature on periprocedural blood pressure (BP) management in acute ischemic stroke and to establish guidelines regarding management of BP. These guidelines are drawn from available evidence and expert opinion. This article reviews the pathophysiologic considerations of BP in ischemic stroke. It also examines the natural history of BP changes during stroke, as well as data on induced BP reduction and hypertension, particularly in light of reperfusion therapy. Finally, the article reviews major ongoing clinical trials for BP management in this setting. Recommendations made in this article may serve as a benchmark for future research in BP management in this patient population. ***Neurology*® 2012;79 (Suppl 1):S199–S204**

GLOSSARY

BP = blood pressure; **CBF** = cerebral blood flow; **CPP** = cerebral perfusion pressure; **DBP** = diastolic blood pressure; **MAP** = mean arterial pressure; **NIHSS** = NIH Stroke Scale; **NINDS** = National Institute of Neurological Disorders and Stroke; **SBP** = systolic blood pressure; **tPA** = tissue plasminogen activator.

INTRODUCTION AND PATHOPHYSIOLOGY Blood pressure (BP) is largely a surrogate for cerebral perfusion pressure (CPP). During acute ischemic stroke, cerebral blood flow (CBF) is predominantly influenced by mean arterial pressure (MAP),[1] as intracranial pressure changes are negligible. A number of other physiologic factors also influence CBF, including oxygen and carbon dioxide partial pressure,[2] cerebral metabolism,[3] temperature,[4,5] and blood viscosity.[6,7] CBF is kept relatively constant across a wide range of perfusion pressures by adjustments in the diameter of vessel resistance, in a process known as autoregulation. In healthy subjects, autoregulation is maintained over a range of CPP (50–150 mm Hg); however, when autoregulation is lost, the relationship between CPP and CBF becomes more linear. As a result of occlusion or severe stenosis, resistance to flow increases, and dilation of arterioles compensates by lowering resistance to flow in the downstream arterial bed.[8,9] A complex series of events, many of which are mediated in part by nitric oxide, ensures CBF compensation for changes in MAP. One of the many effects of ischemia on brain tissue is the loss of autoregulation. In this setting, CBF changes directly with alteration in MAP, rendering ischemic brain vulnerable to minimal variation of the systemic BP. Furthermore, arteriolar tone and consequent changes in CBF are the result of change in the local physiologic milieu, manifested by changes in factors such as extracellular potassium concentration and sustained depolarization. The loss of autoregulation during cerebral ischemia has been extensively demonstrated both in humans[1] and in nonhuman primates.[10]

PET and autoradiography shed light on the series of events that follow cerebral ischemia. In particular, in several species, including humans, several other compensatory mechanisms occur upon reduction of CBF, such as increase in cerebral blood volume, increase in oxygen extraction fraction, and decrease in oxygen consumption. A detailed description of these important phenomena is beyond the scope of this review. In brief, as CBF decreases within the cerebral tissue affected by ischemia, there are regional variations in the execution of these compensatory mechanisms, depending on degree of ischemia, duration of ischemia, degree of collateral circulation, and phylogenetic susceptibility to ischemia of a particular neuronal subpopulation. As a result of these events, the ischemic tissue is divided into a core and a penumbra.[11] The core is considered to be tissue already severely damaged by ischemia and most likely destined to infarction. The penumbra is the ischemic area surrounding the core that has the potential for recovery upon restoration of normal CBF

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values.[12] On the basis of these data, adequate levels of MAP play a critical role in the survival of the penumbral tissue.[10,12,13]

Although the evidence is ample to suggest benefit of MAP maintenance or its elevation during ischemia, it cannot be viewed independently of CBF. BP is a surrogate for CBF and represents a transmural pressure that is distributed throughout the vascular tree. Transmural pressure represents a potential negative influence on transmural rupture (cerebral hemorrhage) and net bulk flow across capillary beds, thereby worsening cerebral edema (Starling's equation) and secondary organ injury to heart and lung. Currently it is unclear how to appropriately weigh the benefits and risks to measure optimal outcome. The benefits and risks are not constant but instead are interdependent on vessel diameter, transmural pressure, and possible transmural rupture.

Recommendation

1. Prospective studies are needed to evaluate CBF via imaging and physiologic continuous monitoring after BP manipulation during acute ischemia.

NATURAL HISTORY OF BLOOD PRESSURE IN ACUTE ISCHEMIC STROKE In patients with ischemic stroke, as many as 60% of patients have a systolic blood pressure (SBP) greater than 160 mm Hg. This elevation can persist for hours to days.[14] Although some portion of elevated BP might be due to a compensatory need to increase CBF, other factors such as stress, pain, discomfort, and intrinsic hypertension likely play a role as well.[15,16] Despite the etiology, BP has a tendency to normalize over 24 to 48 hours.[16,17] With regard to stroke subtype, evidence suggests that lacunar stroke may be associated with higher initial SBP[16] than nonlacunar stroke. Consequently, lacunar stroke–associated BP may decrease over 24 hours to a greater degree than nonlacunar stroke.[18] Most data regarding the association of initial BP on stroke outcome indicate a U-shaped curve.[16,19] Patients with lower BP have worse outcome than those with higher BP. Still, those patients with SBP greater than 180 mm Hg seem to have worse outcome than those with BP in the 150 to 180 range. From the International Stroke Trial Registry, there was either a 3.8% or 17.9% increase in early mortality for every 10–mm Hg change above or below 150 mm Hg, respectively.[16] Others have suggested that initial high BP predicts poor outcome only in combination with impaired consciousness.[1720] However, other data suggest that initial BP is not associated with mortality, but elevated BP over the ensuing 48 hours is associated with higher NIH Stroke Scale (NIHSS) score and greater mortality.[21]

Whether or not high BP is a marker of disease severity or a modifiable mediator with a direct mechanistic relationship to outcome is unclear. We propose that the likely explanation is a component of both. At one extreme, increased BP is a secondary response to cerebral ischemia. As the size and degree of ischemia increase, with individual variability, the BP may increase to support perfusion. However, this response is pathologic, and, like cardiac ventricular remodeling in response to chronic hypertension, this compensatory effort by the body can have pathologic consequences (heart failure or brain failure). The period and setting of brain ischemia are often confounded by other variables that may increase BP independently: anxiety, pain, fever, inflammation, tissue plasminogen activator (tPA)–mediated hemorrhage. Ultimately, clarity with regard to the role of BP rise in the setting of acute ischemia can be answered only with prospective, randomized interventions. Such trials would need to have consistent management strategies for enrolled patients.

It should be noted that it is not clear whether systolic, diastolic, or mean arterial BP is superior for determining outcomes. Although this is unproven, higher spontaneous initial BP might maintain CBF for penumbral tissue. This elevation in BP places patients at an increased risk of hemorrhage, edema, and secondary organ injury. Increased systemic BP increases systemic vascular resistance, thereby increasing myocardial strain and oxygen demand. Increased resistance and myocardial strain can also lead to pulmonary edema, especially in the setting of any volume overload. The correlation of high BP and increased risk of intracerebral hemorrhage is unknown. There was no association with BP and hemorrhage in the European Cooperative Acute Stroke Study (ECASS) I, International Stroke Trial,[16] National Institute of Neurological Disorders and Stroke (NINDS),[23] or Interventional Management of Stroke[24] trials. However, elevated BP is associated with intracerebral hemorrhage after administration of tPA,[25–27] streptokinase,[28] or urokinase.[29] Existing data support an increased risk of cerebral edema when there is simultaneous high BP.[16,18,30] The excessive risk of patients presenting with lower BP is likely secondary to failure to maintain sufficient CBF for penumbral survival. Failure to maintain sufficient CBF is also coupled with higher occurrence of larger stroke, cardioembolic stroke, and heart failure.[16,30]

Recommendation

1. Prospective studies are needed to determine the association of BP and the risk of hemorrhage, cerebral edema, and secondary organ injury, which are based on stroke severity, neurologic deterioration, infarct volume, and other factors associated with poor outcome.

BLOOD PRESSURE MANAGEMENT IN THE SETTING OF THROMBOLYTIC AND REVASCULARIZATION THERAPY In the NINDS recombinant tPA trial, there was a similar incidence of hypertension in the placebo recipients and tPA-treated patients. Hypertensive patients treated with tPA who also received antihypertensive medications had a less favorable outcome at 3 months.[31] In contrast, treatment with recombinant tPA in the NINDS trial was associated with greater BP reduction than placebo.[32] Also, in patients treated with recombinant tPA, higher SBP was associated with persistent occlusion, as assessed by ultrasound, but without worse clinical outcomes at 3 months.[33] Cause and effect cannot be inferred but supported the hypothesis that elevated BP is required to maintain penumbral flow. This evidence is supported by spontaneous reductions in BP after recanalization[34] and increases in infarct volume in the setting of large BP fluctuations without recanalization.[35] Furthermore, hemorrhagic transformation after thrombolytic therapy, consistent with recanalization and the potential for increased brain edema, was associated with a trend toward lower SBP.[36] Conversely, in the setting of thrombolytic therapy, there is significant evidence supporting an association with elevated BP and intracerebral hemorrhage.[26–30]

Recommendations

1. In agreement with the 2007 American Stroke Association Guidelines,[37] SBP should be kept under 180 mm Hg and diastolic BP (DBP) under 105 mm Hg in patients who have received thrombolytic or interventional therapy for the immediate postprocedure period. There are no data to suggest a particular antihypertensive medication to use when it is necessary to lower BP. However, medications that can be rapidly titrated are preferred.
2. Prospective CBF studies are needed to assess any relationship between arterial recanalization and BP that could account for differences in collateral circulation.
3. Prospective randomized trials for BP treatment after recanalization therapy, either drug thrombolysis or mechanical thrombectomy, are needed and should be stratified according to absence or presence of recanalization.
4. Prospective studies are needed to assess the natural history of BP in the setting of interventional therapies. These studies should examine the association of infarct volume, volume of at-risk tissue, collateral flow, recanalization flow, and location of vessel occlusion.

LOWERING BP IN ACUTE ISCHEMIC STROKE Because of the direct relationship between CPP and MAP, lowering BP can diminish CBF to ischemic brain tissue. In a multivariate analysis, accounting for NIHSS score and stroke location,[38] BP reduction in the first 24 hours was independently associated with poor outcome. A Cochrane database review of trials aimed at acute or subacute reduction of BP after ischemic stroke included 5 randomized trials and 218 patients. There was insufficient evidence to support lowering BP in patients with acute stroke.[39] In fact, 3 randomized trials testing nimodipine or β-blockers, BEST,[40] INWEST,[41] and VENUS,[42] all had worse outcomes in the active treatment group. Only interventions in BEST and INWEST were associated with BP lowering. More recently, a trial of candesartan administration within the first 36 hours of stroke (mean time from stroke onset to treatment = 30 hours) compared to 7 days of placebo found no significant difference in BP decline and a significant improvement in mortality and recurrent stroke at 1 year.[43] The lack of effect on BP reduction suggests a mechanism other than BP regulation for this protective effect. In another trial, 40 hypertensive (SBP >140 mm Hg or DBP >90 mm Hg) ischemic stroke patients were randomized to oral lisinopril or placebo within 24 hours of stroke onset. These investigators found significant differences in BP reduction without any difference in clinical outcome. This trial was not powered for clinical outcome.[44] It remains to be proven whether certain classes of antihypertensives might have beneficial effects on stroke outcomes regardless of BP changes.

Recommendations

1. In agreement with the 2007 American Stroke Association Guidelines,[37] for patients not receiving thrombolytic or interventional therapy, BP medication should be withheld for the first 24 hours unless SBP is above 220 mm Hg or DBP is above 110 mm Hg.
2. After 24 hours, BP medications may be restarted safely in a general stroke population, although there are limited high-level data to support this recommendation.
3. Prospective outcome studies are needed to evaluate early initiation of BP therapy in the setting of documented presence or absence of recanalization.
4. Studies are needed to determine whether hypertensive patients with persistent penumbra at 24 hours benefit from the withholding or institution of antihypertensive therapy.

INDUCED HYPERTENSION Because of the desire to improve CBF to penumbral tissue, either through a flow-limiting lesion or through collateral circula-

tion, several groups have attempted to induce hypertension in patients with acute ischemic stroke. For this purpose, α-adrenergic agonists are an attractive choice, as selective vasoconstriction of the peripheral arterial bed can be achieved without involvement of cerebral arteries.[45] In another report,[46] hypertension was prospectively induced in 13 patients within 12 hours of presentation. None of the patients had serious adverse events, and 54% had an improvement of at least 2 points on the NIHSS, attributable to the BP increase. In a retrospective report,[47] 34 ischemic stroke patients with SBP <140 mm Hg were treated with hypertensive therapy (average time of stroke onset to treatment = 13 hours). Early improvement, defined as a 2-point decrease in NIHSS within 8 hours of therapy, was seen in 19% of patients. Treatment was associated with 1 cardiac arrhythmia and 1 fatal intracerebral hemorrhage. Other studies of induced hypertension in the subacute phase, i.e., initiation within 7 days of stroke onset, in patients selected for diffusion–perfusion mismatch have had mixed results.[48,49] The only trial that was randomized demonstrated a significant improvement in NIHSS score for induced hypertension.[48] It is unclear whether these subacute trials of induced hypertension apply in the acute periprocedural time frame for endovascular treatment. Although there appears to be promise for induced hypertension in the acute phase, it is unclear how best to select patients who might benefit and whether a benefit of improved neurologic function will outweigh the potential complications of intracerebral hemorrhage, cerebral or pulmonary edema, and myocardial infarction. Unfortunately, a prior study, Induced Hypertension for Acute Ischemic Stroke, was terminated, in part because of poor enrollment.

Recommendations

1. Arterial hypotension (SBP <120 mm Hg) should be evaluated and corrected, given the strong association with higher mortality.
2. Prospective, randomized trials evaluating induced hypertension are needed. Such trials should also evaluate patient selection on the basis of presenting BP, presence of mismatch, CBF studies, timing of induced hypertension, and agents used. Such trials should include location of vessel involvement, degree of collateral circulation, extent of occlusion, and tissue at risk.

RANDOMIZED TRIALS Only the Controlling Hypertension and Hypotension Immediately Post Stroke (CHHIPS) trial[50] enrolled patients no later than 12 hours from onset into a randomized BP arm. This arm will evaluate induced hypertension in patients presenting with SBP ≤140 mm Hg. Although the remaining trials are important, they are unlikely to address the question of how to manage the vast majority of hyperacute patients, those typically within the 8-hour time window, who are undergoing an interventional procedure for recanalization. Although not strictly a BP trial, the Safety and Efficacy of NeuroFlo Technology in Ischemic Stroke (SENTIS) trial[51] is currently randomizing patients within 14 hours to partial occlusion of aortic outflow or best management. Data from deployment of this intra-aortic device, which spans above and below the renal arteries, suggests that the procedure can elevate CBF without change in systemic BP.[52]

SUMMARY Many patients with acute stroke present with hypertension. There are few data to guide the management of BP within the first 24 hours. Substantial circumstantial evidence suggests that elevated BP might provide needed CBF to penumbral tissue; however, this benefit is associated with higher rates of intracerebral hemorrhage and edema, as well as secondary organ injury to the heart, lungs, and kidneys. Those patients who present with hypotension or relative hypotension (SBP <120–140 mm Hg) are at greatest risk for neurologic deterioration. This group likely has a complex interaction of large strokes and substantial cardiovascular disease. In the absence of data, we agree with the current recommendations of the American Stroke Association for acute management of BP[37] and therefore have highlighted these recommendations and suggested research efforts.

AUTHOR CONTRIBUTIONS

Dr. Sheth: drafting/revising the manuscript, study concept or design. Dr. Sims: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision.

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