

Acute Stroke

Lower Blood Pressure Looks Better and Better

Fernando Eljovich, Cheryl L. Laffer

Not much progress has occurred in guidelines to treat blood pressure (BP) during acute stroke since Sir George Pickering wrote in 1968 about cerebral hemorrhage: "Probably diastolic pressures over 110 are worth reducing to 90 mm Hg. This is a guess, and theoretical arguments could be urged against, or for, different figures," and about ischemic stroke: "There is no evidence that reducing arterial pressure in the acute phase will help."¹

Perhaps the different purposes of treating BP for the prevention of stroke versus managing BP during its acute phase explain this. In the former, BP reduction (and blockade of vasoactive systems) aims at reducing arteriolar remodeling and arterial atherosclerosis, the culprits for both intracerebral hemorrhage (ICH) and ischemic strokes. Its effectiveness has been unequivocally proven; stroke prevention is quantitatively the most beneficial effect of antihypertensive therapy. In contrast, the purpose of managing BP during an acute stroke is to improve outcomes by diminishing the magnitude of the bleed, or the development of edema in the ischemic region, or the extension of tissue necrosis into the penumbra. The physiology of the hypertensive cerebral circulation, before and during a stroke, is complex and contributes to the fact that achieving one of the goals above may conflict with achieving another one.

Normal autoregulation of cerebral blood flow (CBF) maintains it constant over a wide range of mean arterial pressures (MAPs; ≈ 50 through ≈ 150 mm Hg; Figure A). BPs above these limits will produce cerebral edema. In contrast, below the lower limit (located at $\approx 75\%$ of usual MAP), hypoperfusion does not cause immediate ischemia, because the brain is capable of increasing O_2 extraction (thick portion of the curve in the Figure). Cerebral hypoxemia ensues if additional hypotension overwhelms this compensation.

In chronic hypertension, autoregulation is shifted to the right (Figure B). Hence, patients are somewhat protected from developing cerebral edema (ie, hypertensive encephalopathy is more likely with abrupt BP elevation in a previously normotensive individual, eg, acute glomerulonephritis in children or eclampsia, than in severe chronic hyperten-

sion). In contrast, hypertensive subjects have an increased risk of cerebral hypoperfusion with abrupt BP reduction, because the lower limit of autoregulation is also right-shifted.

Knowing the range of autoregulation in a patient with an acute stroke would permit safe targeting of BP reduction, avoiding cerebral hypoperfusion or hyperperfusion. However, this is not possible, because during an acute stroke BP is higher, by an unknown amount, than that preceding the event (Figure C). This pressor effect of stroke is present in 80% of patients and abates over 7 to 10 days. It could be argued that in a hypertensive ischemic stroke, the risk of cerebral edema is less than that of hypoperfusion because of the preceding right-shifted autoregulation, even without knowing its magnitude. Current guidelines match this speculation, because no therapy is recommended unless BP exceeds 220/120 mm Hg in uncomplicated ischemic stroke.² However, the situation is compounded by disrupted autoregulation in the penumbra and ischemic brain (Figure D), where CBF is directly dependent on BP; hence, any BP elevation increases risk of further bleed or cerebral edema, whereas any BP reduction threatens hypoperfusion and extension of the stroke to the area of the penumbra.

In ischemic stroke, several recent studies suggest that current guidelines may underestimate detrimental effects of untreated hypertension and overestimate risk of BP reduction. In a study of 2178 ischemic strokes in Mongolia, the relationship among BP (9.3 hours from event onset), multiple outcomes, and disability was not statistically significant, as it was for 1760 ICHs. However, systolic BP (SBP) >200 mm Hg, that is, 20 mm Hg lower than the current target for treatment, had an odds ratio of 4.36 for adjusted mortality.³ In Tinzaparin in Acute Ischemic Stroke, BP of 1479 patients (24 to 48 hours after onset) was a major determinant of early recurrence and death or dependency at 6 months, despite the fact that subjects with BP $>220/120$ mm Hg were excluded.⁴ In 1722 placebo participants of Virtual International Stroke Trials Archive (enrolled 1.0 to 7.9 hours after the event), odds ratios for neurological impairment at 7 days and functional outcomes at 90 days related to higher SBP at entry, smaller reductions of SBP over the initial 24 hours, and SBP at 24 hours, although >75 mm Hg SBP reduction was associated with worse outcomes.⁵ In the Thrombolysis in Cardiac Arrest Trial (1092 patients recruited within 24 hours of event onset), the relationship between SBP and disability at 3 months was U-shaped, with both SBP ≥ 181 (odds ratio: 2.2) and <136 mm Hg carrying worse prognosis. Best outcomes were observed with 8-hour SBP reduction of 10.0 to 27.2 mm Hg, although the benefit was not observed in subjects older than 76 years. Greater SBP reductions were detrimental, particularly in the elderly and more so if obtained

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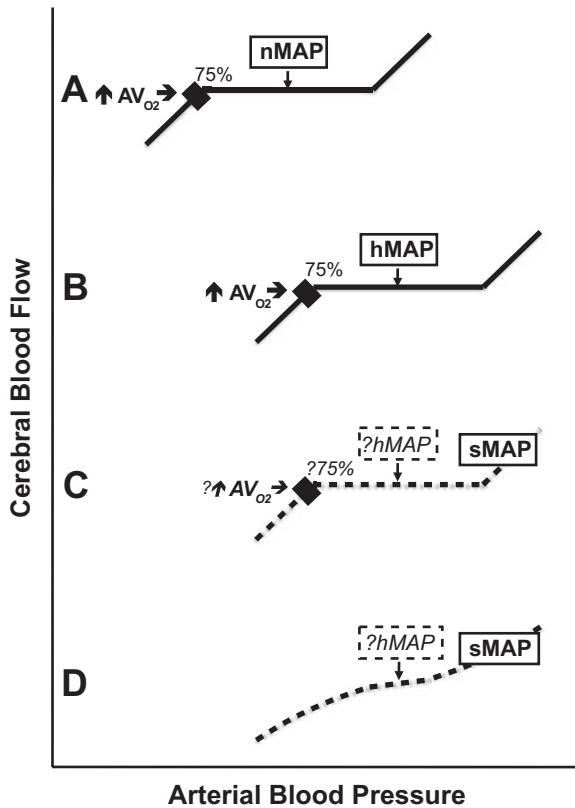


Figure. Schema of autoregulation of cerebral blood flow. MAP indicates mean arterial pressure; n, normotensive; h, in chronic hypertension; s, during acute stroke; 75%, approximate MAP below which cerebral hypoperfusion begins; $\uparrow AV_{O_2}$ and thick portion of the curve, range of hypoperfusion where brain ischemia is prevented by increased O_2 extraction; dashed lines and ?, unknown MAP and range of autoregulation during acute stroke. For discussion, see text.

with antihypertensive therapy. Authors suggested that BP targets currently used for tissue plasminogen activator administration ($<185/110$ mm Hg) could be beneficially extended to all patients within the first 24 hours, if sharp BP reduction is avoided and age is taken into consideration.⁶

Clinical trials favoring intervention at lower BP levels are consistent with a meta-analysis of the effect of 5 families of antihypertensive drugs on CBF. When given to 291 patients in 11 trials, 0.5 to 7.0 days after event onset, MAP reductions of -6.0 to -15.7 mm Hg did not reduce CBF.⁷ Most measurements (single photon emission computed tomography, Xenon-computed tomography, and positron emission tomography-computed tomography) were of hemispheric CBF, but reports on penumbra CBF produced similar results.

Furthermore, unwarranted withholding of treatment may neglect BP-independent beneficial effects of certain drugs. In the Acute Candesartan Cilxetil Therapy in Stroke Survivors Trial ($n=339$), candesartan administration within 24 to 36 hours of event onset reduced 12-month mortality and cardiovascular events by more than half, without BP reduction beyond that by placebo over 7 days.⁸ Benefit was in cardiovascular morbidity/mortality, not in recurrent strokes, leading to the speculation that early protection of cerebral autonomic function may be important for future protection of cardiovascular disease.

In a metaregression analysis of 37 trials, including 9008 patients with ischemic stroke or ICH, the relationship among on-treatment BP (active versus control groups), early (<1 month) and late (90 day) mortalities, and 90-day death/dependency was U-shaped.⁹ Treatment, given within 1 week, involved 13 classes of drugs. Lowest odds ratios for untoward outcomes were obtained with Δ SBPs of -8.1 to -14.6 mm Hg. The Controlling Hypertension and Hypotension Immediately Post-Stroke pilot study ($n=179$) directly tested the effect of lisinopril or labetalol therapy on ischemic stroke and ICH within 36 hours of onset. Target SBP was 145 to 155 mm Hg, to be achieved within 8 hours, with discontinuation if <140 mm Hg. There were no differences between treatments and placebo in combined death/dependency at 2 weeks.¹⁰ However, active therapy halved mortality at 3 months (9.7% versus 20.3%). Despite greater SBP reduction with active therapy (-21 mm Hg versus placebo -11 mm Hg), sustained over 2 weeks, neither deterioration of neurological status over the initial 72 hours nor any increase in serious adverse events was observed.

In this issue of *Hypertension*,¹¹ investigators of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial present further analyses of their data, the first attempt at exploring target BP for patients with acute ICH. They previously published a 24-hour 22.6% smaller proportional growth of hematoma size (CT scan) by aggressive therapy with goal SBP <140 mm Hg (achieved in 1 hour in 42% and in 6 hours in 66% of 203 patients), compared with usual care (1999 American Heart Association guidelines, SBP <180 mm Hg, $n=201$).¹² Patients with compelling indications or contraindications for hypertension treatment, structural cerebral abnormalities, deep coma, and requiring tissue plasminogen activator or neurosurgical intervention were excluded. Participants were randomized ≈ 3.5 hours and started therapy ≈ 4.2 hours after event onset. They were mostly Chinese (95%) and hypertensive (74%), with average BP 181/103 mm Hg (74% required therapy in the usual care versus 98% in the intensive group). SBP throughout the initial 24 hours was 10.8 mm Hg lower in the intensive group. The risk of substantial hematoma growth (defined as $>33\%$ or >12.5 mL) was 36% less in the intensive group (26% versus 40%), independent of age ($>$ or <65), SBP ($>$ or <181), or functional status (National Institutes of Health Stroke Scale $>$ or <9). The effect was larger in subjects randomized within 4 hours of onset ($n=210$, $\Delta-52\%$, intensive: 15% versus usual care: 30%). Early (72-hour) neurological deterioration, 90-day death/dependency, and serious adverse events were not different between groups. In the current publication, the most important observation is that achieved SBP throughout 24 hours (not baseline BP) is the major determinant of hematoma growth at 24 hours, in single and multivariate regression analyses and in covariate adjusted analysis of trends for tertiles of achieved SBP. Based on observed maximum benefit in the lowest tertile (median: 135 mm Hg), the authors cautiously suggest that achieving SBP 130 to 140 mm Hg over the initial 24 hours may be the target of treatment in ICH. Actually, their Figure 3 shows ≈ 20 patients with SBP <130 mm Hg (although this was the limit to stop therapy), without any evidence for a J-curve,

making their suggestion a conservative one. The study cannot be generalized; for example, Chinese subjects have different prevalence and anatomic characteristics of ICH, and severe disease was excluded. Furthermore, despite the recognized prognostic implications of hematoma growth, clinical benefit was not demonstrated, probably because the study was underpowered or its follow-up not long enough. Nonetheless, it provides a strong signal favoring early and aggressive BP reduction in ICH, particularly because the aggressively treated group did not have worse clinical outcomes or adverse events, dispelling concerns about hypoperfusion of the surrounding edematous penumbra.

Ongoing trials in ischemic stroke and ICH, such as Continue or Stop post-Stroke Antihypertensives Collaborative Group (continuation versus interruption of preceding antihypertensive therapy), Scandinavian Candesartan Acute Stroke Trial (candesartan on 6-month outcomes), and The Efficacy of Nitric Oxide in Stroke (transdermal nitroglycerin on death/disability at 90 days) and further research in ICH (Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2, death/dependency at 90 days with the aggressive approach above) will provide additional data. The recently published guidelines from the American Heart Association and American Stroke Association acknowledge that, in ICH, intensive BP lowering is clinically feasible and potentially safe, although target BP and duration of therapy remain unclear.¹³ However, the flurry of research results over the last 2 years already suggests that our current guidelines are too permissive, perhaps even harmful, and will have to be revised soon, recommending judicious BP reduction to lower targets in ischemic stroke and a more aggressive antihypertensive approach to acute ICH.

Disclosures

F.E. is a member of the Novartis Speakers Bureau.

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