



CLINICAL DECISION MAKING

Blood Pressure Management After Acute Ischemic Stroke

Managing blood pressure after acute ischemic stroke requires different approaches before and after reperfusion.

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Introduction

At presentation, 60% to 80% of patients with acute ischemic stroke (AIS) have systolic blood pressures (SBP) over 140 mm Hg.¹⁻³ Patients with preexisting hypertension may have SBP magnitudes higher.^{4,5} Commonly, this *acute hypertensive response* abates within 24 hours, returning to the patient's previous baseline over

several days.⁶ The return to baseline and rapid normalization of BP after arterial recanalization^{7,8} both underscore the physiologic role of the acute hypertensive response.

Despite this natural recovery response, AIS disrupts central autonomic pathways and reduces baroreceptor reflex sensitivity. These disruptions are compounded by comorbid epiphenomena (eg, dehydration, pain, urinary retention, psychological stress, or infection) that can increase circulating catecholamines and inflammatory cytokines, leading to elevated BP.^{6,9,10}

Managing BP in patients with AIS requires understanding:

1. cerebral blood flow (CBF) regulation,
2. the relationship between systemic BP and CBF under normal and ischemic conditions,
3. the evidence relating systemic BP to clinical outcomes in patients with AIS,
4. patients' clinical attributes that affect BP physiology, and
5. contextual advantages and disadvantages of available pharmacologic BP treatments.

Neurologic outcomes in patients with AIS depend on the amount of tissue permanently injured by the ischemic process. Containing infarct volume by preserving the penumbra is

thus a therapeutic priority.¹¹ The penumbra has been thought to result from a competent collateral circulation and to be recoverable by reperfusion (ie, recanalization via intravenous [IV] thrombolysis or endovascular thrombectomy).¹¹⁻¹³

Cerebral Blood Flow Regulation Adaptive Autoregulation

Precapillary vasomotor arterioles (< 400 μ m) display rapid adaptation, via changes in diameter, in response to different stimuli (ie, cerebral perfusion pressure [CPP], serum CO₂ and pH, and cerebral metabolic demands), thereby keeping CBF relatively constant.¹⁴⁻²⁰ This *cerebral autoregulatory mechanism* increases or decreases cerebrovascular resistance if CPP rises above \sim 150 mm Hg or becomes less than \sim 60 mm Hg. Because of this autoregulation, CBF is somewhat "pressure independent" and relatively constant (\sim 60 mL/100 g/min).^{21,22} Above or below these thresholds, however, CPP changes lead to linear and proportional CBF changes, making it pressure dependent.²⁰⁻²² Below the lower limit (\sim 60 mm Hg), tissue will become ischemic as CBF decreases. Effects above the upper limit are more complex; maximal vasodilation increases endothelial permeability, with consequent edema and even hemorrhage, increased intracranial pressure (ICP), rebound reduction in CPP, and ischemia from tamponade. Complicating this further, the thresholds vary under diverse conditions.²⁰⁻²³

- Sympathetic activation and chronic hypertension causes a rightward shift of the autoregulatory curve.^{23,24}
- Chronic hypercapnia elevates curve, narrowing plateaus.¹⁶
- Autoregulation seems to change more in response to CPP increases vs decreases.^{17,25}

Adaptive autoregulation seems to depend on myogenic and chemical (ie, pressure and metabolic) changes, and, to a lesser degree, autonomic stimulation.²⁶ It is thought that, at



rest, vasodilatory and vasoconstrictive effects are balanced, creating vasoactive tone.²⁷ Regional differences in arterial and arteriolar innervation, superimposed on baseline tone, lead to adaptive CBF variations to meet distinct metabolic demands of specific territories; this is termed neurogenic coupling.^{26,28,29}

Therapeutic Targets

Not only does ischemia make CBF pressure dependent, it also affects tissue oxygen delivery (DO_2) and uptake (VO_2), with proportional reduction in DO_2 .^{20,21,30} Neural tissue compensates by increasing oxygen extraction fraction (OEF) to maintain VO_2 levels and tissue viability.³⁰ There is an upper limit of OEF, however, and beyond this, reduced CBF and DO_2 result in insufficient VO_2 and ischemic tissue injury.³⁰

Because CBF is pressure dependent in ischemia and VO_2 is CBF-dependent, VO_2 is also pressure-dependent during ischemia. To improve tissue perfusion, CBF must be addressed, by targeting CPP. This can be done by targeting the mean arterial BP (MABP) component of systemic BP because:

$$CPP = MABP - ICP.$$

In patients with AIS, reducing risk of hemorrhagic complications must also be prioritized, and elevated systemic BP is associated with poor outcomes.³¹⁻³³ Treatment decisions must always consider systemic BP that determines risk of lost endothelial integrity and vascular rupture. Together, MABP and systemic BP can be a composite therapeutic target. Parenthetically, despite being addressed in guidelines, the relative importance of diastolic BP (DBP) is likely minor, related only to calculating MABP and pulse pressure.³²⁻³⁵

A Therapeutic Continuum

Reperfusion is a critical part of the standard of care for patients with AIS and the most direct approach to improve CBF, VO_2 , and DO_2 .³⁵ Reperfusion is, however, only a milestone on a therapeutic continuum. Prevailing circumstances of each point on that continuum determine how BP is best managed.

The brain of anyone with AIS can be thought of as 2 distinct compartments, each with different flow physiology, requirements, and attributes. The ischemic compartment, the primary therapeutic target, has no autoregulation, is pressure-dependent CBF, and has OEF at risk of being exhausted.³⁶⁻³⁸ The non-ischemic compartment, unaffected brain tissue, has preserved autoregulation and pressure-independent flow. Throughout the therapeutic continuum, the simultaneous effects of managing BP on both compartments must be considered.

Before Reperfusion

During prereperfusion (onset of the ischemic process to achievement of tissue reperfusion), management should focus on preserving penumbral viability, primarily by optimizing

collateral flow.^{12,13} Aggressive attempts to lower BP worsen ischemia and must be avoided. Intravascular volume must be maintained because dehydration is present in 30% to 60% of patients with AIS and is associated with worse outcomes.³⁹⁻⁴² Current guidelines advocate correction of hypotension and hypovolemia (Class I evidence). However, hypotension is not well defined, and reduction of SBP (< 185 mm Hg) is also recommended in patients receiving IV thrombolysis (Class I) or for whom endovascular recanalization is planned (Class IIa).³⁵

After Reperfusion

The post-reperfusion interval is more complicated with less predictable and less uniform physiologic patterns, largely due to variability in timing and success of revascularization and its consequences on tissue integrity. Complete reperfusion (ie, Thrombolysis in Cerebral Infarction [TICI] score = 3) has different implications than partial reperfusion (ie, TICI = 1 or 2a), and both are influenced by timing of revascularization.

In the postreperfusion interval, the priority shifts from improving collateral perfusion by elevating MABP to preventing further damage to the injured vascular bed from elevated SBP. Management strategies must be tailored to individual cerebrovascular scenarios and how these evolve over time. When reviewing the literature, these considerations must also be taken into account, because most studies do not clearly define what the prereperfusion and postreperfusion intervals were during protocol implementation, rendering conclusions somewhat artificial and impractical.

Empiric Evidence and Therapeutic Priorities

A single optimal therapeutic target for BP is likely an oversimplification; this may explain negative clinical trial results for BP reduction in patients with AIS and the harmful effects of early administration of antihypertensive agents (Table). The 3 trials of BP reduction⁴³⁻⁴⁵ focused on safety and prevention of complications over effectiveness. The other 2 studies,^{46,47} focused on protecting the penumbra from intracellular calcium influx with an agent with powerful antihypertensive effects. In all 5 studies, therapeutic intervals varied considerably and were considered homogeneous for each study. BP levels that qualified patients for inclusion in the first 3 studies varied. In 2 studies patients with SBP of 140 mm Hg (who would not be treated in clinical practice) were included.^{43,44} In the 2 neuroprotective studies,^{46,47} the baseline BP reported would typically not result in active BP treatment, and effects of treatment on BP during the acute period were not reported. In summary, existing data regarding active treatment of elevated BP in patients with AIS are of poor quality and difficult to translate into practical bedside application.

Euvolemia, An Easy and Effective Therapeutic Target

As noted, dehydration is present in 30% to 60% of



TABLE. CLINICAL STUDIES REPORTING A DIRECT OR INDIRECT EFFECT OF BLOOD PRESSURE REDUCTION ON ISCHEMIC STROKE OUTCOMES.

Study sample size	Patient inclusion criteria	BP inclusion criteria mm Hg	Intervention	Target BP mm Hg	Conclusions regarding intervention
ANTIHYPERTENSIVE STUDIES WITH DIRECT BLOOD PRESSURE REDUCTION					
ACCESS ⁴⁵ n = 339	18-85 y AIS within 36 h of onset	SBP ≥ 200 or DBP ≥ 110 within 6-24 h of admission OR SBP ≥ 180 or DBP ≥ 105 within 24-36 h of admission	Oral candesartan 4-16 mg/d titrated to maintain target BP for 7 d vs placebo	< 160/100	No reduction in disability; reduced 12-month mortality and cardiovascular events
PROFESS ⁴³ (subgroup) n = 1,339	>55 y OR 50-54 y with multiple vascular risk factors AIS within 72 h of onset	SBP 121-180 and DBP ≤ 110	Oral telmisartan 80 mg/d indefinitely vs placebo	< 140/90	No reduction in functional dependency or death at 30 d
CATIS ⁴⁴ n = 4,071	≥ 22 y AIS within 24 h of onset	SBP 140-220 and DBP < 120	Antihypertensive medication vs no antihypertensive for 7 d	10-25% below baseline then < 140/90	No reduction in death or major disability at 14 d or discharge
NEUROPROTECTIVE STUDIES WITH SECONDARY BLOOD PRESSURE REDUCTION					
INWEST ⁴⁷ n = 295	≥ 40 y AIS in carotid territory within 24 h of onset	None	IV nimodipine 1 or 2 mg/h for 5 d followed by oral nimodipine 30 mg 4x/d for 16 d vs placebo	None	Worse neurologic and functional outcome at 21 d, 12 and 24 w; dose-dependent worse outcomes
Kaste et al ⁴⁶ n = 350	16-69 y AIS in carotid territory within 48 h of onset	None	Oral nimodipine 120 mg/d for 21 d vs placebo	None	No improvement in functional outcome; increased fatalities at 3 months
Abbreviations: AIS: acute ischemic stroke; BP, blood pressure; d, days; DBP, diastolic blood pressure; h, hours; IV, intravenous; SBP, systolic blood pressure; w, weeks; y, years.					

patients with AIS and clearly associated with poorer outcomes.³⁹⁻⁴² Dehydration is also relatively easy to treat, with potentially high payout, considering that administering IV isotonic crystalloid is safe and relatively easy for most patients. Intravascular volume restoration should be carried out independently of BP because the hypertensive response may partly result from dehydration.^{48,49} Before reperfusion, rehydration will benefit collateral circulatory support of the ischemic penumbra. After reperfusion, maintaining intravascular volume is likely necessary because other aspects of care (eg, osmotic diuresis caused by most contrast agents) reduce intravascular volume.

Avoid Blood Pressure Extremes

Although aggressive BP reduction after AIS is generally not recommended, ignoring excessively high SBP is also counterproductive. The existing literature supports a U-shaped relationship between BP at admission and poor outcomes, including mortality.^{2,31,32,34,50} Because information about how

BP evolved, was treated, or influenced treatment in these studies is not available, however, it remains unclear exactly what BP range is safe and effective.

Multiple published series provide a heterogeneous amalgamation of data on different aspects of elevated BP in patients with AIS, with most studies addressing whether BP at admission correlates with neurologic outcome and/or mortality.^{2,31-34,50,51} Several studies^{2,31,32,34,50} document negative effects of excessively high³³ or low⁵¹ SBP. Despite the lack of benefit for active BP treatment in clinical trials (Table), it is possible to conclude that the trials demonstrate it is safe to treat elevated BP after acute ischemia has passed.⁴³⁻⁴⁵ In 2 series that include enough information to infer optimal BP range at admission, MABP of 100 mm Hg to 140 mm Hg and SBP of 150 mm Hg to 200 mm Hg were most likely to be associated with survival.^{32,34}

Blood Pressure Requirements Evolve

As discussed, CPP requirements vary and evolve, with mod-



estly elevated systemic BP measurements being somewhat necessary during the prereperfusion interval,^{2,31,32,34,50,51} leading to popularization of the term *permissive hypertension* that is poorly defined and not well studied. Allowing BP in the optimal range defined earlier (MABP 100-140 mm Hg; SBP 150-200 mm Hg) for patients with AIS should provide the best chance for a good outcome.

Once arterial recanalization and primary brain tissue reperfusion have started, the need for higher-than-normal BP dissipates, and excess is likely to increase increased capillary permeability and extravasation of fluid (ie, edema) and/or blood products (ie, hemorrhage). During the post-reperfusion interval, elevated SBP for 24 hours after IV thrombolysis is associated with poor outcome,⁵² particularly if there are symptomatic intracerebral hemorrhages.⁵³ The reported optimal SBP in these studies approximates 140 mm Hg to 150 mm Hg, which is lower than specified by studies of BP at admission and supports the postulated benefit of BP decline after reperfusion.

In the ENCHANTED^a trial early and intensive SBP reduction to 130 mm Hg to 140 mm Hg after IV thrombolysis is being compared to the standard guideline-driven therapeutic target of 180 mm Hg.⁵⁴ The obvious limitation of ENCHANTED is that it is not possible to predict if or when reperfusion is achieved with IV thrombolysis. Lowering BP aggressively but potentially before reperfusion risks aggravating ischemia because CBF pressure-dependent before reperfusion. Managing BP theoretically should be easier in patients treated endovascularly, because the exact time and degree of reperfusion is known. Unfortunately, no major clinical trial of endovascular treatment systematically addressed BP management or specified target SPB after reperfusion, although BP over 180/110 mm Hg was used as an exclusion criteria,⁵⁵⁻⁶¹ consistent with existing guidelines for IV thrombolysis at the time of the trials.⁵⁵⁻⁶¹ None of these studies excluded patients because of their BP on presentation, and the 4 that specified systolic pressures be recorded on arrival at the hospital listed values that were only modestly elevated.⁵⁵⁻⁶¹

A Practical Approach

Although recommendations from experts⁶² and published guidelines⁶³ provide little practical guidance for BP management in AIS, it is possible to construct a management protocol using the concepts discussed (Figure).

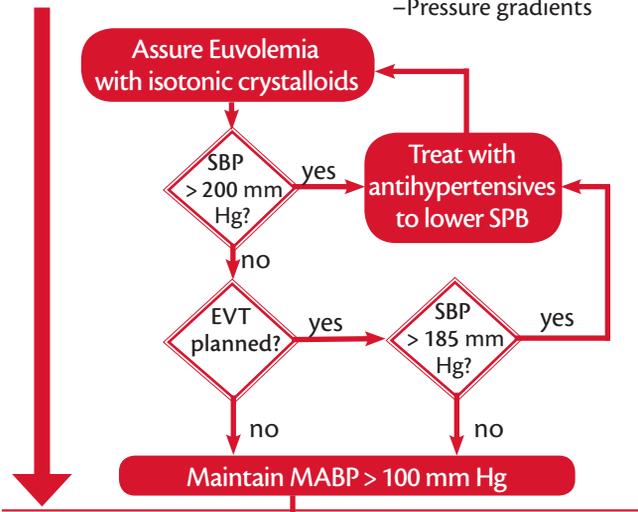
The Pre-Reperfusion Interval

The most reasonable strategy for BP management, from the patient's arrival through actual reperfusion, is akin to what has been termed *permissive hypertension*.

1. Assure euvoemia using isotonic crystalloids.
2. Do not use antihypertensives unless SBP exceeds 200 mm Hg (185 mm Hg if IV thrombolysis considered)
3. Assure that MABP remains higher than 100 mm Hg.

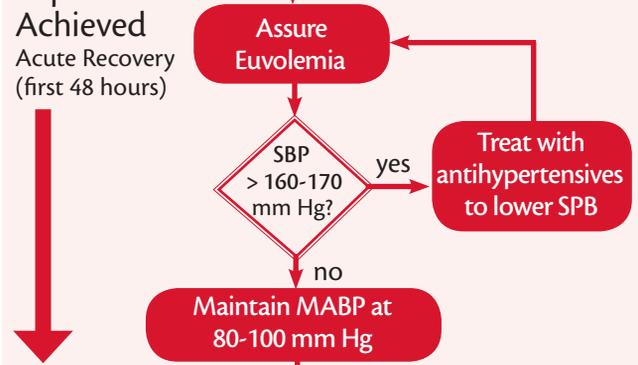
Pre-Reperfusion Ischemia Present

Special Considerations:
–Pseudohypertension
–Pressure gradients



Reperfusion Achieved Acute Recovery (first 48 hours)

MABP = CPP + ICP



Continued Recovery Prevention of Secondary Stroke

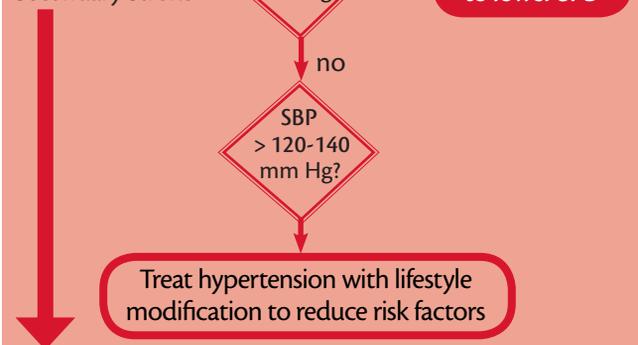


Figure. A management protocol constructed from principles discussed, available evidence, and expert recommendations. Abbreviations: CPP, cerebral perfusion pressure; EVT, endovascular treatment; ICP, intracranial blood pressure; MABP, mean arterial blood pressure; SPB, systolic blood pressure.

a. Enhanced control of hypertension and thrombolysis stroke study (NCT 01422616).



These 3 steps maximize chances of maintaining CPP to protect the ischemic penumbra, while reducing the risk of unnecessarily elevated SBP that is clearly associated with worse outcomes.^{32,34} Although there may be a temptation to reduce SBP below 185 mm Hg in patients who will be treated endovascularly (without concurrent or pre-emptying IV thrombolysis), the existing literature does not support this.⁶⁴ As a therapeutic threshold for SBP in those having endovascular procedures, 200 mm Hg may be more reasonable both because it makes MABP above 100 mm Hg (the desired lower threshold) more likely, and because BP will likely be reduced during the procedure by medications used for sedation. Additionally, once reperfusion is achieved, BP will be reduced spontaneously^{7,8} or can be carried out expeditiously with a wider safety margin.

When antihypertensives are required before reperfusion, medications should be easily titrated, administered parenterally, with a short half-life, and without neurologic side effects. Labetalol, nicardipine, clevidipine, hydralazine, and enalaprilat are recommended.³⁵ Labetalol and the dihydropyridine calcium-channel blockers have the important advantage of continuous infusion that facilitates a steady state, potentially avoiding damaging effects of exaggerated BP variability.^{65,66} Irrespective of the agent used, the importance of closely and continuously monitoring BP in patients with AIS given antihypertensives cannot be overemphasized, particularly during transitions of care (eg, emergency department to catheterization laboratory to neurointensive care unit).^{35,62,63}

The Post-Reperfusion Interval

Near-obsessive attention to euvolemia must continue after reperfusion, perhaps even more so because patients are often affected by the osmotic diuretic effect of contrast agents used in diagnostic procedures.

The most recent guidelines^{67,68} for patients treated with IV thrombolysis from the National Institute of Neurological Disorders and Stroke (NINDS) and European Cooperative Acute Stroke Study (ECASS-III) recommend careful BP reduction (185/110 mm Hg) before starting IV thrombolysis and maintenance of systemic BP below 180/105 mm Hg for 24 hours after administration (Class I).³⁵ The practical drawback is as noted for the ENCHANTED study; it is not possible to know if, when, and how much reperfusion was achieved. This makes it nearly impossible to judge what MABP will be too low to protect the ischemic penumbra before reperfusion or what SBP is high enough to risk hemorrhage after reperfusion. The recommended upper threshold (ie, 180/105 mm Hg) can only be evaluated in light of the existing literature.^{32,34,53} The most recent data on how BP in the 24 hours after IV thrombolysis influences the risk of hemorrhagic transformation suggest that 180/105 mm Hg and resulting MABP (130 mm Hg) are likely too high.⁵³ In contrast, an upper SBP threshold of 170 mm Hg is relatively consistent with available data on SBP at admission and

outcomes for patients with AIS,^{32,34} making it most reasonable to maintain SBP at 160 mm Hg to 170 mm Hg (approximating the MABP to 115 mm Hg) after IV thrombolysis. Higher SBP is neither necessary nor safer⁵³ and increases risk of hemorrhage by approximately 12% to 14% per each 10 mm Hg.⁵³

Although this range is wholly compatible with the current guidelines,³⁵ in accordance with the understood limitations of this approach, close monitoring to determine if and when reperfusion is achieved should be an inherent component of any treatment protocol. This is a difficult and important task because once reperfusion is achieved the benefit of elevated SBP and MABP is greatly reduced, and therapeutic strategy should shift to prevention of fluid and blood product extravasation and management of any hemorrhage that occurs.

After endovascular reperfusion, management of BP, although not fundamentally different in principle, is simplified by knowing the procedural outcome. Patients who undergo thrombectomy have higher hemorrhagic complication rates when the maximum recorded SBP is elevated after the procedure.⁶⁹ Predictably, this is more pronounced in those with successful recanalization (ie, TIC1 = 2b-3), probably because they no longer require high BP-driven collateral circulatory support of the penumbra. Available data suggest that, if recanalization is successful (ie, TIC1 = 2b-3), SBP levels should be maintained below 160 mm Hg.⁶⁹ Patients whose procedure has been less successful (ie, TIC1 = 0-2a) are able to withstand SBP similar to that proposed for patients post-thrombolysis (ie, 170 mm Hg).⁶⁹ These values are compatible with current guidelines³⁵ and expert recommendations.⁶²

Mean Arterial Blood Pressure in Management Protocols

We have concentrated primarily on management of SBP both because it is the major determinant of positive outcomes and patient safety must come first, and because most literature on BP management in AIS is centered on SBP. Nevertheless, SBP does not exist in isolation, and the major determinant of CPP (and thus CBF and perfusion) is MABP. As discussed, brain perfusion becomes pressure-dependent and prone to ischemia if CPP drops below 60 mm Hg under normal conditions, and at higher thresholds under conditions of chronic hypertension (autoregulation preserved) or acute arterial occlusion (autoregulation impaired). Thus, CPP levels above 60 mm Hg to 80 mm Hg seems reasonable in patients with AIS. A simple approach is possible because most patients with AIS have normal ICP during the acute period and,

$$\text{CPP} + \text{ICP} = \text{MABP}$$

Thus, optimal MABP is 85 mm Hg (70 + 15) for perfusion under specific conditions (70 mm Hg = mean minimal CPP when range = 60-80 mm Hg and 15 mm Hg = normal ICP upper limit [20 cm H₂O = 15 mm Hg]).²⁰ This approach also



makes it possible to recalculate patients' needs under varying conditions. Needless to say, such calculations must be accompanied by careful consideration of whether or not reperfusion occurred and was complete and successful, as well as the safe and allowable levels of SBP described earlier.

End-Game: Blood Pressure Reduction for Prevention

As part of the continuum of care, BP management eventually shifts from recovery after ischemia to prevention of secondary stroke with risk-factor modification. With few exceptions, after 48 hours of treatment, lowering systemic BP to the individual's baseline level and gradual reducing it to normal improves long-term outcomes of mortality and overall cardiovascular health.⁴³⁻⁴⁵ An approach tailored to each clinical situation, with consideration of all of the variables discussed in this article, seems to represent the most reasonable path.

Special Considerations

Translesional Gradients. Patients with AIS may also have underlying pathology (eg, high-grade stenosis upstream from an atherothromboembolic infarction) that can display translesional pressure gradients of 30 mm Hg to 40 mm Hg. In these cases, basing treatment decisions solely on brachial artery BP measurement can lead to excessive compromise of CPP and worsen the ischemic process. Translesional pressure gradients must be taken into consideration in applicable scenarios. This is among the reasons why hyperacute neurovascular imaging is essential for patients with AIS. Although there is no easy method for estimating translesional pressure gradients, several groups are working on defining how they may effect care.^{70,71}

Pseudohypertension. In patients with significant atherosclerosis, arterial wall rigidity—identifiable at the bedside—may cause falsely elevated BP measurements.⁷² Although earlier publications retrospectively estimated prevalence of pseudohypertension as 5% to 7% of adults over age 60,^{72,73} more recent reports suggest prevalence may be as high as 50%.⁷⁴ Care must be exercised when measuring BP in patients with severe atherosclerosis because the values obtained may be falsely elevated, putting these patients at risk of overtreatment.

Conclusions

Management of systemic BP during AIS—a major neurologic emergency—represents an important, complex, and challenging aspect of care. A thorough understanding of cerebrovascular physiology and how it is impaired under conditions of ischemia is critical to the clinical decision-making process. Protecting and preserving penumbral tissue by optimizing collateral flow before therapeutic reperfusion requires sufficiently elevated MABP, achieved by tolerating higher than normal SBP. Along the therapeutic time continuum, after successful reperfusion, lowering SBP to a range associated with improved outcomes then becomes the primary management target. ■

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