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STROKE (H.C. DIENER, SECTION EDITOR)

Management of Blood Pressure After Acute Ischemic Stroke

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Abstract

Purpose of Review The present manuscript examines the significance of blood pressure elevation in patients with acute ischemic stroke, the physiologic principles worthy of consideration during its treatment, and the recent empirical evidence that should guide management protocols. It also provides a sound and practical approach to treatment along the time continuum, with particular relevance to reperfusion strategies.

Recent Findings The existing evidence shows that both insufficient and excessive blood pressures are detrimental to the outcome of patients with acute ischemic stroke. This "U-shaped" relation, however, relates to measurements at the time of presentation, and clinical studies lack detail and specificity relative to differential measurements along the time continuum, particularly prior to and following reperfusion. Extrapolating from recent series, it is possible to construct treatment protocols balanced for effectiveness and safety.

Summary The management of blood pressure after acute ischemic stroke is an important, complex, and challenging aspect of care, requiring a thorough understanding of cerebrovascular physiology. Along the time continuum, the therapeutic priorities start with the preservation of penumbral tissue prior to reperfusion and then follow with the limitation of the damaging effects of excessive blood pressure readings after reperfusion, optimizing the chances of improved outcomes.

Keywords Hypertension · Ischemic stroke · Acute management · Thrombolysis · Thrombectomy · Revascularization

Introduction

The prevalence of blood pressure elevation early in the course of acute ischemic stroke (AIS) is extremely high, with 60–80% of patients displaying systolic blood pressures (SBP) in excess of 140 mmHg at the time of presentation [1•, 2, 3] and values considerably greater in those with pre-ictal hypertension [4, 5]. In the past, this phenomenon has been considered an *acute hypertensive response* and has been defined as "two or more measurements (at least five minutes apart) during the first 24 hours, of a SBP > 140 mmHg or diastolic blood pressure (DBP) > 90 mmHg". Typically, elevated blood pressures gradually defervesce over several days and trend down to individual baseline values [6]. The pathogenesis of such a time course has been debated through the years, with speculations that it represents (a) a natural physiologic response to the acute neurologic insult, (b) the direct result of injury to specific neural structures, (c) an indicator of poorly controlled pre-ictal hypertension, or (d) a combination of all of these. Its potential role in the natural homeostatic response to ischemic brain injury is supported by (a) the spontaneous reduction to baseline blood pressure levels in most stroke patients over time and (b) the rapid normalization of blood pressure measurements following arterial recanalization [7•, 8]. Conversely, the resulting disruption of central autonomic pathways and reduction of baroreceptor reflex sensitivity which can result from AIS, compounded by co-morbid epiphenomena (e.g., dehydration, pain, urinary retention, psychological stress, or infection), can also enhance the levels of circulating catecholamines and inflammatory cytokines, resulting in abnormally elevated blood pressure [6, 9, 10].

In light of these considerations, the management of blood pressure in patients with AIS demands that clinicians understand (a) the mechanisms by which cerebral blood flow (CBF)

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is regulated, (b) the relationship between systemic blood pressure and CBF, both under normal and ischemic conditions, (c) the empirical evidence demonstrating how systemic blood pressure levels influence clinical outcomes in patients with AIS, (d) the various clinical attributes of stroke patients that affect blood pressure physiology, and (e) the advantages and disadvantages of the various pharmacologic agents available for blood pressure treatment. Moreover, since the ultimate neurologic outcome in this population greatly depends on the amount of tissue permanently injured by the ischemic process, reducing infarct volume though preservation of the penumbra constitutes a critical therapeutic priority [11••]. Tissue viability within the ischemic penumbra depends on collateral circulatory competence, and its long-term preservation on the success of reperfusion strategies (i.e., recanalization via intravenous thrombolysis or endovascular thrombectomy) [11••, 12, 13].

Normally, CBF is maintained at relatively constant levels by the rapid adaptation of pre-capillary vasomotor arterioles, whose diameters (< 400 μm) change in response to a variety of stimuli (e.g., cerebral perfusion pressure (CPP), serum CO_2 and pH, cerebral metabolic demands) [14, 15•, 16–19, 20••]. This mechanism, known as *cerebral autoregulation*, operates by increasing (i.e., arteriolar vasoconstriction) or decreasing (i.e., arteriolar vasodilation) cerebrovascular resistance in response to CPP measurements within a range that approximates ~ 60–150 mmHg. As a result, CBF is considered "pressure independent" under normal conditions, readily maintaining levels that approximate 60 mL/100 mg/min (Fig. 1) [21, 22]. Outside of the range specified, changes in perfusion pressure are accompanied by linear and proportional changes in CBF, making it "pressure dependent" (Fig. 1) [20••, 21, 22]. Therefore, continued CPP decrements below the lower limit of autoregulation (i.e., ~ 60 mmHg) are likely to result in steadily worsening ischemia due to progressive CBF reduction. Conversely, however, the effect of CPP exceeding the upper autoregulatory limit is considerably more complex, since maximal compensatory vasodilation is bound to produce increased endothelial permeability, with consequent edema (even hemorrhage), increased intracranial pressure, rebound reduction in CPP, and ischemia from "tamponade" physiology. It is exceedingly difficult to predict the slope of any line that represents the change of CBF as a function of changes in CPP, not only for any particular patient but also within a specific set of circumstances, thereby hindering any attempt at forecasting the marginal effect on CBF from any therapeutic manipulation of the CPP. The problem is even more complicated by the fact that, on one hand, the CBF-CPP relationship is linear under conditions of ischemia (i.e., pressure dependency) and, therefore, the magnitude and speed of the effect is given by either of these two formulas:

$$m = \Delta\mathrm{CBF}/\Delta\mathrm{CPP} \text{ or } m = \tan\theta$$

where m is the slope of the line that represents the flow/pressure function, and θ is its angle of incline. Conversely, the normal autoregulatory curve has been shown to be more dynamic than the traditional view shown in Fig. 1 [20••, 21, 22], but generally matching an *increasing*

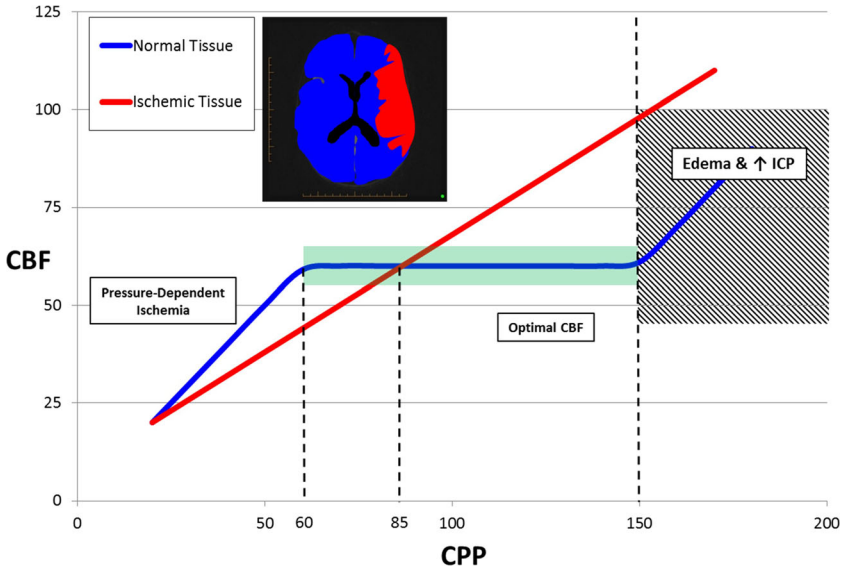

Fig. 1 Pressure-flow relationship in concurrent normal and ischemic brain tissue ("two compartment model"). Normally, CBF remains relatively constant and independent of CPP within certain boundaries (blue figure and line). Ischemic tissue, on the other hand, displays a more linear, pressure-dependent relationship (red figure and line). The function that determines the magnitude of this relationship, as illustrated by the slope of the graph, is uncertain and subject to individual variations. Note that unwanted reduction of blood flow from optimal levels (green) can occur at materially different levels of CPP (e.g., 85 vs. 60 mmHg), underscoring the different considerations for therapeutic targets (see text for detail). CBF, cerebral blood flow; CPP, cerebral perfusion pressure; ICP, intracranial pressure

monotonic cubic polynomial function. As such, its variable slope can only be derived by calculating its first derivative which, in its simplest form would be given by the formula:

$$f'(\mathrm{CPP}) = 3\mathrm{CPP}^2$$

Moreover, the autoregulatory plateau has been shown to have pronounced variability under diverse circumstances [20••, 21–23], its limits influenced by different factors, such as sympathetic activation and chronic hypertension shifting the entire curve to the right [23, 24], and chronic hypercapnia causing an elevation of the curve with narrowing of its plateau [16]. In addition, autoregulation appears to be selectively more responsive to increments rather than decrements of CPP [17, 25]. The poorly understood mechanisms underlying autoregulation depend on myogenic (i.e., pressure), chemical (i.e., metabolic), and autonomic stimulati [26•]. At rest, balanced endothelial vasodilatory and vasoconstrictive influences of nitrous oxide, and endothelin, thromboxane and angiotensin II, respectively [27], create a baseline "vasoactive tone" as a background for superimposed adaptive variations of CBF required to meet distinct metabolic demand within specific territories (i.e., "neurogenic coupling"), driven by regional differences in arterial and arteriolar innervation [26, 28, 29].

Additional relevant concepts relate to changes in tissue oxygen delivery (DO_2) and uptake (VO_2) triggered by the ischemic process (Fig. 2) [20••, 21, 30]. As CPP decreases, CBF becomes pressure dependent, and a proportional reduction in DO_2 becomes apparent [30]. Initially, affected neural tissue maintains VO_2 levels constant by increasing oxygen extraction fraction (OEF) as a compensatory mechanism, effectively preserving tissue viability (Fig. 2) [30]. However, once the compensatory limit of OEF increase is reached, further reduction of CBF and DO_2 is accompanied by progressive VO_2 decline and, ultimately, ischemic tissue injury [30]. Thus, the following logical relationship becomes apparent:

Since CBF in ischemic tissue is pressure-dependent, and VO_2 *is flow-dependent, then* VO_2 *is also pressure-dependent (i.e., if A = B and B = C, then A = C).*

Therapeutic decisions that target maintenance of effective CBF levels depend on the mean arterial blood pressure (MABP) as their critical variable, since the driving force of tissue perfusion is CPP, which is given by the formula:

$$\mathrm{CPP} = \mathrm{MABP} - \mathrm{ICP}$$

where CPP is cerebral perfusion pressure, MABP is mean arterial blood pressure, and ICP is intracranial pressure. Nevertheless, blood pressure treatment following AIS is also geared at reducing the risk of hemorrhagic complications, forcing clinicians to *always* take into account the SBP, as this is the variable associated with the risk of hemorrhagic complications and with poor outcomes [31–33]. Consequently, it is best to consider the dyad of MABP and SBP as a composite therapeutic target, in order to optimize the achievement of sound physiologic and clinical goals. In this context, the importance of DBP is minor and largely connected to the calculation of MABP and pulse pressure [32, 34].

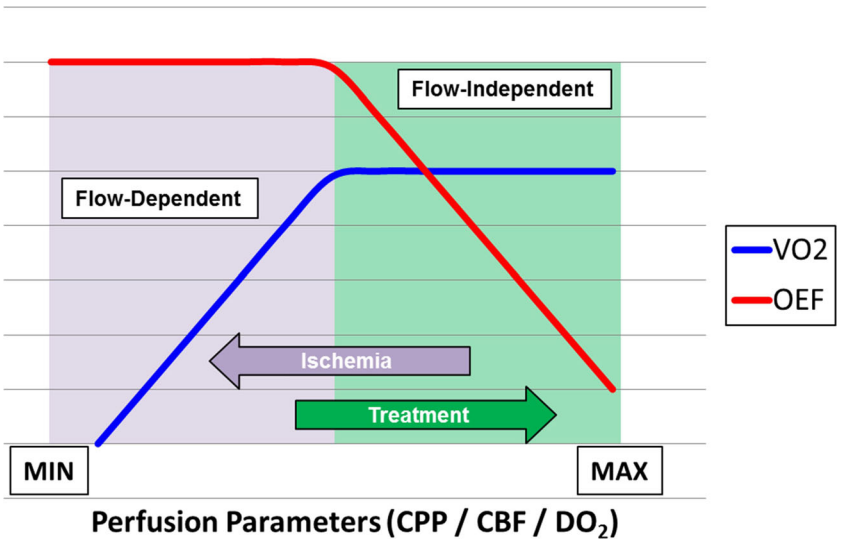

Fig. 2 Effect of progressive decline of cerebral perfusion on tissue oxygenation. As tissue perfusion decreases, evidenced by reduction of any of the relevant parameters, oxygen uptake (VO_2) is maintained somewhat constant by compensatory increases in oxygen extraction fraction (OEF), effectively representing a flow-independent state (green). Once a maximal level of OEF is reached, further reductions in perfusion lead to progressive decline in tissue VO_2 due to a flow-dependent state (violet). Thus, ischemia moves tissue conditions to the left of the graph, while the treatment goals are to move them to the right (see text for detail). CPP, cerebral perfusion pressure; CBF, cerebral blood flow; DO_2 tissue oxygen delivery

Fundamental Considerations

The most direct approach to improving CBF, DO_2, and VO_2 involves the application of reperfusion strategies (i.e., intravenous thrombolysis and endovascular thrombectomy), which are currently important components of the standard of care of AIS [35••]. That said, revascularization constitutes a milestone within the therapeutic time continuum (Fig. 3), and the management of blood pressure must be compatible with the hemodynamic conditions prevailing at any one point in time (Fig. 3).

Practically, the brain of any patient with AIS may be seen as comprising two distinct "compartments," each with its own underlying flow physiology, attributes, and requirements (Fig. 1): (a) an *ischemic compartment* (i.e., the primary therapeutic target) is devoid of autoregulation (RED in Fig. 1), displays pressure-dependent CBF, and its OEF is at risk of insufficient compensatory effect (Fig. 2) [36–38] and (b) a *non-ischemic compartment* that encompasses all of the remaining (i.e., unaffected) brain tissue (blue in Fig. 1), characterized by pressure-independent CBF and preserved autoregulation (Figs. 1 and 2). Accordingly, the blood pressure management must consider the simultaneous effects of any treatment step on *both* compartments.

During the *pre-reperfusion interval* (i.e., between the onset of the ischemic process and the achievement of tissue reperfusion), the emphasis of management focuses on preservation of penumbral tissue viability (Fig. 3) [12, 13]. Aggressive "normalization" of blood pressure measurements must be avoided, as this may lead to worsening of the ischemic process. On the other hand, attention to the intravascular volume is exceedingly important, particularly because of the prevalence of dehydration in AIS patients (i.e., 30–60% of cases) and its association with worse outcomes [39–42]. Current guidelines recommend correction of hypotension and hypovolemia (class I), but they fail to define these very well [35••]. They also recommend the reduction of SBP to less than 185 mmHg in patients treated by intravenous thrombolysis (class I), and to "reasonably" consider doing so to ≤ 185 mmHg in those for whom endovascular recanalization is planned (class IIa) [35••]. None of the published guidelines, however, properly address blood pressure management *following* revascularization and reperfusion.

The *post-reperfusion interval*, is somewhat more complicated, and involves less predictable and less uniform patterns of physiology, all subordinate to the variable degrees of timing and success of revascularization, as well as their consequences on tissue integrity. Complete final reperfusion (i.e., thrombolysis in cerebral infarction (TICI) = 3) clearly has different implications than partial success (i.e., TICI = 1 or 2a), although they are both influenced by the timing of revascularization. Management post-reperfusion necessitates a priority shift, from the possible beneficial effect of elevated MABP on collateral support, to the potentially damaging effect of excessive SBP on a partially injured vascular bed. Thus, therapeutic strategies must be tailored to each clinical scenario and often modified depending on their evolution over time. These arguments must also be considered while reviewing the literature, since most studies lack a clear definition on how these intervals were managed during protocol implementation, rendering the conclusions somewhat capricious and impractical.

Review of the Empirical Evidence

There is not a single blood pressure value that could be considered the "optimal" therapeutic target, and such an unwarranted oversimplification probably explains the negative results of clinical trials of deliberate blood pressure reduction in patients with AIS and the harmful effects of "early" administration of pharmacologic agents with an inherent antihypertensive effect (Table 1) [43–45, 46••, 47••, 48, 49]. The

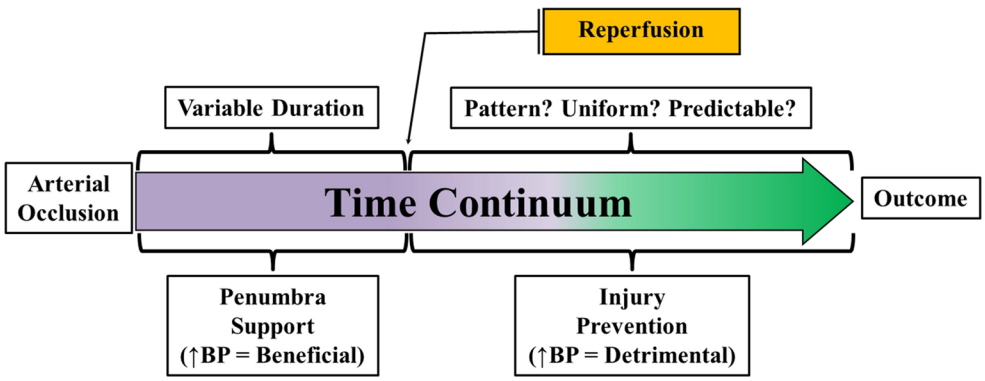

Fig. 3 Clinical priorities for blood pressure management along the time continuum. Following arterial occlusion, prior to reperfusion, the priority is one of support of the ischemic penumbra. During this *pre-reperfusion interval* elevated blood pressure (i.e., "permissive hypertension") may be beneficial since they promote improved collateral circulation (particularly mean arterial blood pressure). Once reperfusion has been achieved, however, excessive blood pressure (particularly systolic) endangers the tissue by promoting vascular injury and hemorrhagic changes. During this *post-reperfusion interval*, blood pressure control should be the norm. BP, blood pressure

Table 1 Clinical studies reporting a direct or indirect effect of blood pressure reduction on ischemic stroke outcomes

Study	Patients	BP inclusion criteria	Intervention	Target BP	Conclusions
Antihypertensive studies with direct blood pressure reduction					
ACCESS [43]	•$n = 339$ •Age 18–85 years •AIS within 36 h of onset	•SBP ≥ 200 mmHg or DBP ≥ 110 mmHg within 6–24 h after admission or •SBP ≥ 180 mmHg or DBP ≥ 105 mmHg within 24–36 h after admission	•Oral candesartan 4–16 mg/day titrated to maintain target BP for 7 days vs. placebo	•BP < 160/100	•No reduction in disability in the intervention arm •Reduced rates of mortality and cardiovascular events at 12 months in the intervention arm
PRoFESS [44] (subgroup)	•$n = 1360$ •Age > 55 years or 50–54 years with multiple vascular risk factors •AIS within 72 h of onset	•SBP 121–180 mmHg and DBP ≤ 110 mmHg	•Oral telmisartan 80 mg/day indefinitely vs. placebo	•BP < 140/90	•No reduction in functional dependency or death at 30 days
CATIS [45]	•$n = 4071$ •Age ≥ 22 years •AIS within 24 h of onset	•SBP 140–220 mmHg and DBP < 120 mmHg	•Antihypertensive medication (ACE-I, CCB, D) to reduce to target BP within 24 h and maintain target BP for 7 days vs. no antihypertensive medication for 7 days	•Reduction of baseline BP by 10–25% within 24 h and maintain BP < 140/90 mmHg for 7 days	•No reduction in death or major disability in the intervention arm at 14 days or hospital discharge
ENCHANTED [46••]	•$n = 2196$ •Age ≥ 18 years •AIS within 4.5 h of onset	•SBP ≥ 150 mmHg	•Aggressive SBP reduction vs. guideline-driven protocol	•SBP 130–140 mmHg vs. < 180 mmHg	•Reduction of intracerebral hemorrhage in the aggressive treatment group, but no measurable effect on outcome
RIGHT-2 [47••]	•$n = 1149$ •Age ≥ 18 years •AIS within 4 h of onset	•SBP ≥ 120 mmHg	•Pre-hospital transdermal nitroglycerin	•Not specified	•No improvement in functional outcome in the treatment group
Neuroprotective studies with secondary blood pressure reduction					
INWEST [48]	•$n = 295$ •Age ≥ 40 years •AIS in carotid territory within 24 h of onset	•None	•IV nimodipine 1 or 2 mg/h for 5 days followed by oral nimodipine 30 mg 4×/day for 16 days vs. placebo	•No target BP	•Worse neurological and functional outcome significantly at 21 days, 12 weeks, and 24 weeks in the intervention arm •Worse outcomes in a dose-dependent manner in the intervention arm
Kaste et al. [49]	•$n = 350$ •Age 16–69 years •AIS in carotid territory within 48 h of onset	•None	•Oral nimodipine 120 mg/day for 21 days vs. placebo PP	•No target BP	•No improvement in functional outcome in the intervention arm •Increased rate of fatalities at 3 months in the intervention am

AIS acute ischemic stroke, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *BP* blood pressure, *ACE-I* angiotensin-converting enzyme inhibitors (used as first line), *CCB* calcium channel blockers (used as second line), *D* diuretics (used as third line)

following facts are evident in Table 1: (a) only the two most recent trials of primary blood pressure reduction were designed to assess efficacy [46••, 47••], while the previous three primarily targeted safety and prevention of complications [43–45]; (b) the two other studies had the aim of "protecting" the ischemic penumbra from intracellular calcium influx, unfortunately using an agent with powerful antihypertensive effects [48, 49]; (c) the therapeutic intervals were chosen somewhat haphazardly, varied considerably (i.e., 36–72 h), and were considered homogeneous for each study; (d) the blood pressure levels chosen for inclusion in the first five studies [43–45, 46••, 47••] varied significantly, with four of them including SBPs that would never lead to treatment in clinical practice (e.g., 120–140 mmHg) [44, 45, 46••, 47••]; and (e) the two neuroprotective studies [48, 49] reported baseline blood pressure measurements that would typically not result in active blood pressure treatment and failed to report the effects of treatment on blood pressure during the acute period. Thus, the existing empirical information about the effect of actively treating elevated blood pressure following AIS is of poor quality and difficult to translate for bedside application. Still, the following priorities are supported by the available evidence and constitute reasonable underpinnings for a pragmatic therapeutic approach:

1. *Euvolemia: easy and effective therapeutic target*. Dehydration is very prevalent in patients with AIS and is associated with worse outcomes [39–42]. As such, the effortless and safe nature of administering isotonic crystalloid to most patients makes dehydration an easy target of opportunity, with a relatively high payout. Intravascular volume optimization should be pursued even in patients with elevated blood pressure, since the latter may partly result from the dehydration itself [50, 51]. Achieving euvolemia during the pre-reperfusion interval is geared at positively influencing collateral circulatory support of the ischemic penumbra. Following reperfusion, however, intravenous fluid administration is likely to counteract the deleterious effects of other ubiquitous aspects of care (e.g., the osmotic diuresis caused by most contrast agents).
2. *Blood pressure extremes: always to be avoided*. Despite the fact that aggressive reduction of blood pressure following AIS is generally not recommended, ignoring excessively high values of SBP is also counterproductive. The literature has consistently shown a "U-shaped" relationship between admission blood pressure and poor outcomes [2, 31, 32, 34, 52]. Unfortunately, there is little information about the evolution of blood pressure after admission, or how changes relate to the treatment administered. Thus, what blood pressure range should be adopted as both *effective* and *safe*?

   The existing literature on the issue of elevated blood pressure in patients with AIS constitutes an amalgamation of heterogeneous aspects of the subject. The majority have addressed the effect of admission blood pressure levels on outcome [2, 31–34, 52, 53]. Several uncovered the "U-shaped" relationship mentioned earlier [2, 31, 32, 34, 52], while others explicitly documented the negative effects of excessively high [33] or low [53] SBP. From the only two series with sufficient information to infer an "optimal" admission blood pressure range, a MABP in the 100–140 mmHg range and a SBP between 150 and 200 mmHg represent the values most likely to be associated with survival (Table 2) [32, 34].
3. *Blood pressure requirements change over time*. The CPP requirements vary along the therapeutic continuum, and modestly elevated systemic blood pressure is considered desirable during the *pre-reperfusion interval* [2, 31, 32, 34, 52, 53]. This has led to the popularization of the term "permissive hypertension" which, although widely adopted, it is poorly defined and inadequately studied. Nonetheless, maintaining blood pressure readings within the "optimal" ranges specified (i.e., MABP = 100–140 mmHg and SBP = 150–200 mmHg) is likely to improve the chances of a good outcome (Table 2) [32, 34].

   Following arterial recanalization, with tissue reperfusion, a higher-than-normal blood pressure is no longer necessary, and any excess may result in increased capillary permeability, with extravasation of fluid (i.e., edema) and/or blood products (i.e., hemorrhage). Thus, we must consider the effects of blood pressure during the *post-reperfusion interval*. Following intravenous thrombolysis, elevated SBP within the first 24 h has been associated with poor outcome [54], particularly increasing the risk of symptomatic intracerebral hemorrhage [55]. The reported "optimal" SBP approximates 140–150 mmHg, which is lower than the range specified earlier for admission blood pressures (Table 2), and validates the beneficial effect of blood pressure declining after reperfusion. Most recently, neither the Enhanced Control of Hypertension ANd Thrombolysis StrokE StuDy (ENCHANTED) nor the Rapid Intervention with Glyceryl trinitrate in Hypertensive stroke Trial (RIGHT-2) showed a material improvement in overall outcome in AIS patients treated more aggressively than it is common in practice (Table 1) [46••, 47••]. The design limitation of both ENCHANTED and RIGHT-2 is obvious: *The administration of an intravenous thrombolytic agent does not allow the prediction of the time required for reperfusion, or if it will even occur*. Therefore, lowering SBP aggressively prior to reperfusion carries the risk of

Table 2 Mortality risk relative to admission blood pressure levels in two major clinical trials (see text for details)

Study	Metric	Low limit	Insufficient	Optimal	Excessive	High limit
Okumura et al. [32]	SBP[a] (mmHg)	< 130	130–150	150–170	170–210	> 210
	MABP[b] (mmHg)	< 90	90–100	100–116	116–146	> 146
	Mortality RR (30 days)	2.02	1.21	1.0	1.13	1.57
Stead et al. [34]	SBP (mmHg)	< 155		155–220		> 220
	MABP (mmHg)	< 100		100–140		> 140
	Mortality RR (90 days)	1.7–2.1		1.0		1.9–2.1

RR relative risk

[a] Rounded to the nearest multiple of ten

[b] Calculated from the published data

worsening the ischemic process, while CBF remains pressure dependent. In addition, the differences in SBP between treatment and control groups in both studies averaged 5–6 mmHg [46••, 47••], possibly too small of a difference to detect any beneficial effect [55].

Blood pressure management in the context of reperfusion strategies should theoretically be easier in patients treated endovascularly, since the exact time and degree of reperfusion is known. However, the major clinical trials did not systematically addressed this issue (Table 3) and, in fact (a) none of their protocols included specific target levels of blood pressure to be achieved following reperfusion, and yet, (b) nearly all of them listed "uncontrolled" blood pressures above 180/110 mmHg as an exclusion criterion [56–60, 61•, 62•]. Moreover, none of them reported patients being excluded from enrollment based on their level of blood pressure on presentation and the four that detailed the SBP recorded on arrival to the hospital, listed values that were only modestly elevated [56–60, 61•, 62•]. Since current recommendations by experts [63•], or published guidelines [64••], provide little practical guidance, we shall use the concepts discussed above to suggest a management approach.

Practical Management Steps

Pre-reperfusion Interval

The most reasonable strategy during the interval between onset and documented reperfusion is the so-called permissive hypertension, which should (a) assure euvolemia using isotonic crystalloids, (b) not actively administer antihypertensive agents unless the SBP exceeds 200 mmHg (185 if intravenous thrombolytic treatment is being considered), and (c) assure that the MABP remains higher than 100 mmHg (Table 4). Such an approach is geared at maintaining CPP at levels sufficient to protect the ischemic penumbra, while reducing the risk of an unnecessarily elevated SBP, clearly associated with worse outcomes [32, 34]. During this interval, the temptation to reduce the SBP below 185 mmHg in patients to be treated endovascularly (without concurrent or pre-emptying intravenous thrombolysis) should be curbed since the existing literature does not support such a practice [65•]. Using 200 mmHg as a SBP threshold seems more reasonable since (a) this value is more likely to be associated with a MABP above 100 mmHg (the desired lower threshold), (b) blood pressure is likely to be reduced during the endovascular procedure by

Table 3 Blood pressure criteria used for enrollment and management in the major thrombectomy studies

Study	Exclusion BP Level (mmHg)	Median SBP (mmHg)[b]	Patients (ENDO)	IV TPA (%)	Baseline HTN (%)	Post-reperfusion BP target (mmHg)
MR CLEAN [56]	> 185/110	146	233	203 (87.1)	NS	Not specified
ESCAPE [57]	Not specified	147	165	119 (72)	105 (63.6)	Not specified
REVASCAT [58]	> 185/110[a]	142	103	70 (68)	62 (60.2)	Not specified
SWIFT PRIME [59]	> 185/110[a]	150	98	98 (100)	NS	Not specified
EXTEND IA [60]	> 185/110[a]	NS	35	35 (100)	21 (60)	Not specified
DAWN [61•]	> 185/110[a]	NS	107	5 (5)	83 (78)	Not specified
DEFUSE 3 [62•]	> 185/110[a]	NS	92	10 (11)	NS	Not specified

NP blood pressure, *SBP* systolic blood pressure, *ENDO* endovascular treatment group, *HTN* hypertension, *NS* not specified

[a] Specified as "uncontrolled," allowing for treatment and reduction prior to enrollment

[b] Measured on arrival

Table 4 Blood pressure targets and thresholds for the various therapeutic intervals

Interval	Sub-category	Target volume status	Target SBP (mmHg)	Target MABP (mmHg)	Comments
Pre-reperfusion	IV thrombolysis	Euvolemia	< 185	≥ 100	"Permissive hypertension"
	No IV thrombolysis (including endovascular)	Euvolemia	< 200	≥ 100	
Post-reperfusion	Complete reperfusion	Euvolemia	≤ 160	≥ 85	Documented by imaging
	Incomplete reperfusion (including post-thrombolysis)	Euvolemia	≤ 170	≥ 90	Circumstantial or evident
Long term	Subacute and chronic	Euvolemia	≤ 130	≥ 85	Beware of "pseudohypertension" and gradients

medications used for sedation, and (c) once reperfusion is achieved, blood pressure will be reduced spontaneously [7•, 8] or can be actively lowered with a wider safety margin.

Pharmacologic intervention prior to reperfusion is best accomplished using an agent that (a) is administered parenterally, (b) has a short half-life, (c) is easily titrated, and (d) has no unwanted neurologic side effects. The drugs widely recommended are labetalol, nicardipine, clevidipine, hydralazine, and enalaprilat [35••]. An important advantage of labetalol and the dihydropyridine calcium channel blockers is that they can be administered by continuous infusion, facilitating a steady state and potentially avoiding the damaging effects of exaggerated blood pressure variability on stroke outcome [66, 67]. Irrespective of the agent utilized, close and continuous monitoring of blood pressure cannot be overemphasized, particularly during transitions of care (e.g., emergency department to catheterization laboratory to neurointensive care unit) [35••, 63•, 64••].

Post-reperfusion Interval

The same near-obsessive attention to euvolemia must continue during this interval, particularly since the contrast agents during the diagnostic procedures invariable induce profound osmotic diuresis (Table 4). Presently, management in patients treated with intravenous thrombolysis is primarily guided by criteria from the National Institute of Neurological Disorders and Stroke (NINDS) intravenous thrombolysis [68] and the third European Cooperative Acute Stroke Study (ECASS-III) [69] trials, specifying a "careful" blood pressure reduction to SBP < 185 mmHg and DBP < 110 mmHg prior to initiation of IV thrombolysis and maintenance of BP < 180/105 mmHg for 24 h after administration (class I) [35••]. The practical drawback of this strategy is identical to that of the ENCHANTED and RIGHT-2 studies: *The inability to know if, when, and how much reperfusion has been achieved*. This makes the tasks of (a) avoiding worsening of the ischemic penumbra by excessively decreasing MABP prior to reperfusion and (b) risking reperfusion hemorrhage after reperfusion by unnecessarily allowing excessive SBP values, near impossible to complete within a reasonable degree of certainty. A reassessment of the recommended upper threshold (i.e., 180/105 mmHg) in light of the existing literature suggests that such value is likely excessive [32, 34, 55]. In fact, the reported upper SBP threshold of 170 mmHg is consistent with the available data on admission SBP and stroke outcomes [32, 34]. Moreover, the calculated MABP for the 180/105 mmHg threshold (i.e., 130 mmHg) appears similarly excessive when compared with the same published datasets [32, 34]. Thus, it seems reasonable to maintain an upper SBP limit of 160–170 following intravenous thrombolysis (Table 4), particularly since (a) higher systolic pressure values are neither necessary nor safer [55]; (b) the risk of hemorrhagic transformation increases by approximately 12–14% per 10 mmHg aliquot [55]; (c) such SBP values would commonly translate into a MABP of approximately 115–116 mmHg, well within the "optimal" range indicated in the literature [32, 34]; and (d) they are wholly compatible with the current guidelines [35••] and probably quite safe [46••]. In accordance with the understood limitation of this approach, closely monitoring patients to document reperfusion should be an inherent component of any protocol, invariably requiring serial imaging (Fig. 4). Once reperfusion is confirmed, and the incentive for maintaining the SBP and MABP higher than "normal" diminishes, a shift in hemodynamic priorities is particularly helpful when hemorrhagic transformation has occurred (Fig. 4 and Table 4).

Blood pressure following endovascular reperfusion is made considerably easier by the knowledge of the procedural outcome. Patients who undergo thrombectomy also have higher hemorrhagic complication rates when the maximally recorded SBP following the procedure is elevated [70••]. Predictably, the effect is more pronounced in those with successful procedural recanalization (i.e., TICI = $2b - 3$) and, in such instances, SBP should be maintained below a threshold of approximately 160 mmHg [70••]. However, those patients whose procedure has not been "successful" (i.e., TICI = $0 - 2a$) are able to withstand (and will require) SBP similar to those proposed for patients post-thrombolysis, and which approximates 170 mmHg [70••], and also compatible with current guidelines [35••] and expert recommendations (Table 4) [63•].

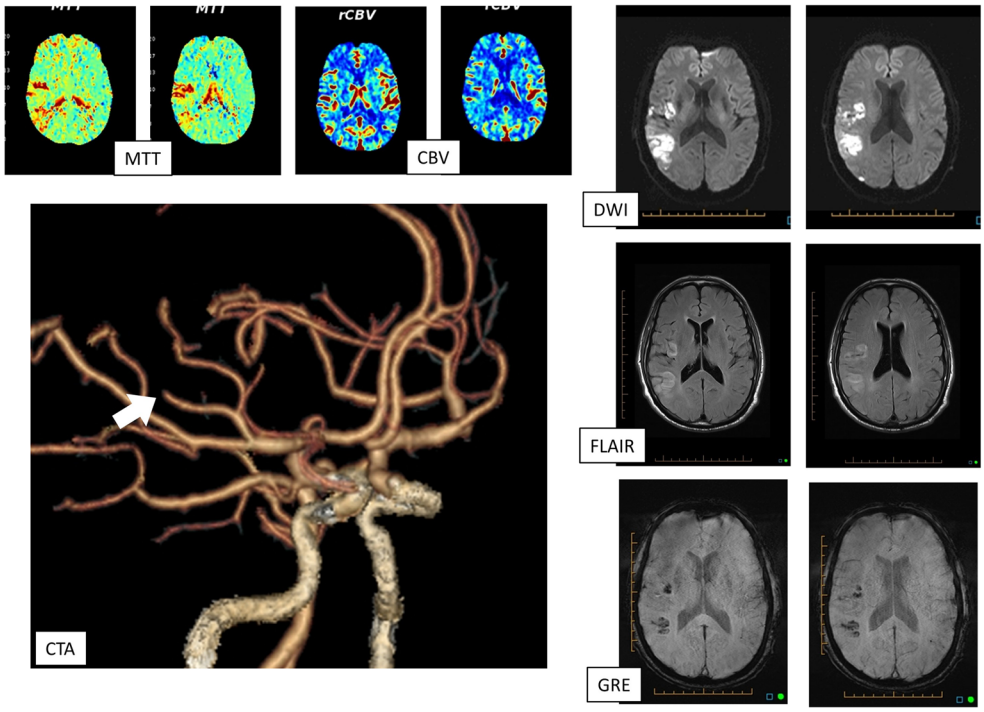

Fig. 4 Imaging studies of a patient with a cortical cardiogenic embolism, treated with intravenous thrombolysis. Upon admission, the CTP scan demonstrates the ischemic penumbra (MTT) in the right hemisphere, with minimal evidence of an ischemic core (CBV). The admission CTA demonstrates the occluded cortical branch (arrow). Approximately 24 h following the administration of intravenous alteplase, the MRI shows evidence of ischemia in a pattern consistent with a fragmented embolus (DWI and FLAIR sequences), with petechial hemorrhagic transformation along the cortical ribbon (GRE sequence). CTP, computed tomography perfusion; CTA, computed tomography angiogram; MTT, mean transit time; CBV, cerebral blood volume; DWI, diffusion-weighted imaging; FLAIR, fast low angle inversion recovery; GRE, gradient refocusing echo

Mean Arterial Blood Pressure in Management Protocols

The reasons for having concentrated on strategies for SBP management are that (a) patient safety should be a primary consideration in the context of reperfusion strategies, (b) the major determinant of safety is the SBP, and (c) the bulk of the literature is centered on SBP measurements after AIS. Nevertheless, SBP does not exist in isolation, and the major determinant of CPP is the MABP, forcing us to address its role in the management of these patients. Brain perfusion becomes pressure dependent and prone to ischemic injury once the CPP drops below 60 mmHg under normal conditions and at higher thresholds under conditions of chronic hypertension (autoregulation preserved) and acute arterial occlusion (autoregulation impaired) (Fig. 1). Thus, maintenance of CPP at levels above 60–80 mmHg seems reasonable in patients with AIS, and a simple approach follows:

Given that

$$\mathrm{CCP} = \mathrm{MABP} - \mathrm{ICP}$$

Then

$$\mathrm{CCP} + \mathrm{ICP} = \mathrm{MABP}$$

Since most AIS patients have normal ICP during the acute period, it is possible to substitute estimated values, for example,

$$70 + 15 = 85$$

where 70 is the average minimally needed CPP (i.e., range = 60–80), and 15 is the upper limit of normal of the intracranial pressure in mmHg (i.e., 20 cmH_2O = 15 mmHg) [20••]. This approach provides a method for estimating the minimal value of MABP that may be required (or tolerated) in order to perfuse brain tissue under specific conditions. Should conditions were to change, this approach makes it possible to recalculate the new requirements. Needless to say, such calculations must be accompanied by careful consideration of (a) whether reperfusion has been achieved or not; (b) if achieved, whether reperfusion has been complete and successful or not; and (c) the safe and allowable levels of SBP described earlier (Table 4).

End-Game: Blood Pressure Reduction for Prevention

Finally, along the continuum, blood pressure management eventually shifts from the therapeutic realm of ischemia

recovery to secondary prevention via risk factor modification. After the first 48 h of treatment, and only with a few exceptions, lowering systemic blood pressure to each patient's baseline levels, with gradual reduction to normal measurements, leads to improved outcomes in terms of mortality and overall cardiovascular health (Table 1) [43–45]. Therefore, an approach tailored to each clinical situation seems to represent the most reasonable path (Table 4).

Special Considerations

Two final topics that merit discussion are (a) pathologic pressure gradients and (b) "pseudohypertension." The first one pertains to concurrent underlying pathology accompanied by pressure gradients (e.g., a high-grade carotid stenosis upstream from an atherothromboembolic infarction, capable of displaying translesional pressure gradients of 30–40 mmHg). In such instances, making treatment decisions solely on the basis of blood pressure measurements obtained from the brachial artery can easily lead to excessive compromise of CPP and worsening of the ischemic process, underscoring the importance of hyperacute neurovascular imaging. There is presently no easy method for estimating translesional pressure gradients, but several groups continue to work on defining their impact [71•, 72•].

"Pseudohypertension," a pathologic condition described by Osler in 1892 consists of spuriously elevated blood pressure readings in patients with significant atherosclerosis. The rigidity of arterial walls, identifiable at the bedside, causes the non-invasive measurement of blood pressure to be erroneously elevated in comparison to the true intraluminal pressure [73]. Earlier publications retrospectively estimated its presence in 5–7% of elderly patients [73, 74], but more recent reports suggest that it can reach 50%, when assessed prospectively in certain subpopulations [75]. The implication is obvious: Care must be exercised when measuring blood pressure in elderly patients with severe atherosclerosis, since the values obtained may be falsely elevated, risking overtreatment.

Conclusions

AIS is a major neurologic emergency and the management of systemic blood pressure in its context represents an important, complex, and challenging aspect of care. A thorough understanding of cerebrovascular physiology and its impairment under conditions of ischemia is critical to the decision-making process in these clinical scenarios. Protecting and preserving penumbral tissue by optimizing collateral flow prior to therapeutic reperfusion requires maintenance of sufficiently elevated MABP by tolerating higher than "normal" levels. Along the therapeutic time continuum, following successful reperfusion, limiting the potential damaging effects of exaggerated SBP then becomes the primordial management target. The results of optimal blood pressure levels have been associated with improved outcomes.

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Compliance with Ethical Standards

Conflict of Interest Zachary Bulwa, Camilo R. Gomez, Sarkis Morales-Vidal, and José Biller each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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