REVIEW

Management of Elevated Blood Pressure After Stroke Thrombectomy for Anterior Circulation

Kexin Wu[1,2]
Zhencheng Xiong [ID][3,4]
Yasuo Ding [ID][1,2]

[1]Postgraduate School, Dalian Medical University, Dalian, People's Republic of China; [2]Department of Neurosurgery, Taizhou People's Hospital, Taizhou, People's Republic of China; [3]Institute of Medical Technology, Peking University Health Science Center, Beijing, People's Republic of China; [4]Peking University Third Hospital, Beijing, People's Republic of China

Abstract: Thrombectomy is superior to intravenous thrombolysis for patients with large vessel occlusion in acute ischemic stroke, but nearly half of the patients still experience poor functional outcomes. Elevated blood pressure (BP) is widely observed in acute ischemic stroke, and BP may be one of the modifiable parameters that can potentially influence the outcomes; however, only observational studies exist to support current guidelines, and the recommended range for BP after thrombectomy is too wide to meet the clinical requirement. Randomized controlled trials are therefore needed to better understand the relationship between BP and outcomes after thrombectomy. In this review, we introduce the current management of BP after thrombectomy and several aspects of postthrombectomy BP management that should be resolved in future clinical trials.

Keywords: acute ischemic stroke, mechanical thrombectomy, blood pressure, hypertension, outcomes

Introduction

Stroke is the third leading cause of death and DALYs (disability-adjusted life-years) globally, with a huge financial and social burden.[1,2] Approximately 84.4% of the total number of prevalent strokes are ischemic strokes,[3] and large vessel occlusion (LVO) is detected in more than one-third of acute ischemic strokes (AISs).[4,5] Several randomized controlled trials (RCTs) have demonstrated the benefit of thrombectomy over intravenous thrombolysis, and the successful recanalization rates were improved to 70–80%;[6–10] however, nearly half of the eligible patients suffered from poor functional outcomes (mRS score >2 at 90 days) despite successful treatment with mechanical thrombectomy (MT).[11]

Various attempts have been made to ensure that patients with LVO are able to acquire maximum benefits from MT, including prehospital screening and dispatching systems to minimize transport time, emergent stroke severity rating scales and neuroimaging evaluations to promptly select qualified patients, and improved reperfusion therapy and catheters to ameliorate complete reperfusion rates. However, even in patients with acute cerebral LVO who are recanalized in a timely manner, the functional outcome is not always a success. Many factors can influence the functional outcome, but not all can be controlled. Acute stroke teams are incapable of determining the existing status of patients who are undergoing MT, such as the infarct and penumbra volume, collateral status, underlying diseases and time of stroke onset. Still, there are some parameters with the potential to improve functional outcomes that stroke teams can easily manipulate including anesthesia, oxygen, temperature, blood sugar and BP.

Correspondence: Yasuo Ding
Department of Neurosurgery, Taizhou People's Hospital, Taizhou, People's Republic of China
Email doctordys@126.com

As one of the modifiable parameters, BP elevation (>140/ 90 mmHg) is widely detected during the early stage of ischemic stroke, occurring in approximately 80% of patients,[12–14] which may serve as a compensatory response to better sustain brain perfusion. BP management in patients with LVO may be roughly divided into 3 sections: before, during and after MT. BP targets of the 3 periods are controversial, especially the third. Because sympathetic innervation is less common in the posterior circulation and would generate different BP,[15] herein, we focus on the management of elevated BP after thrombectomy for anterior circulation.

Guidelines and Practices
Guidelines
The 2019 update to the 2018 AHA/ASA acute ischemic stroke management guideline recommends maintaining patient BP at ≤180/105 mm Hg during and for 24 h after MT and <180/ 105 mm Hg once successfully recanalized.[16] The lack of RCTs in this management guideline is continuously confusing clinical practice; until now, no clear line has connected BP and outcome. Between 2010 and 2014, 5 RCTs (ESCAPE, REVASCAT, SWIFT PRIME, MR CLEAN and EXTEND IA) demonstrated the effectiveness of endovascular thrombectomy over standard care, but even in the protocols of these large RCTs, limited data on the optimal BP goal were reported. The ESCAPE protocol supplied additional instructions that proposed controlling systolic blood pressure (SBP)≥150 mmHg while the artery remained occluded and regulating the BP to a normal level once recanalized. The REVASCAT protocol recommended that BP should be tightly controlled to less than 185/110 mmHg during the first 24 h and less than 160/90 mmHg if TICI ≥2b is achieved. Additionally, DAWN and DEFUSE 3 extended the MT time window to more than 6 h with critical imaging selection criteria a few years later, but only DAWN additionally recommends maintaining SBP<140 mmHg during the first 24 h after MT while reperfusion is achieved and keeping the BP target similar to the control group if reperfusion is not reached (Table 1).[17]

Practices
Current guidelines do not have explicit directions for post-MT BP management and cannot satisfy the needs of clinical practice given its wide range. Most stroke centers divide post-MT patients into a successful reperfusion group and an unsuccessful reperfusion group according to the perfusion status. Patients from each of the 2 groups would subsequently accept one of the following 7 target BP management schedules in light of the

Table 1 Blood Pressure Target in Thrombectomy-Based Randomized Controlled Trials

RCT	Occlusion	Reperfusion
ESCAPE	SBP≥150mmHg	Normal
REVASCAT	<185/110 mmHg	BP<160/90 mmHg
SWIFT PRIME	≤ 180/105 mm Hg	
MR CLEAN	Not mentioned	
EXTEND IA	Not mentioned	
DAWN	Similar as control group	SBP<140mmHg
DEFUSE 3	Not mentioned	

Abbreviations: RCT, randomized controlled trial; BP, blood pressure; SBP, systolic blood pressure.

respective therapeutic regimens: SBP<120 mm Hg, 120–139 mm Hg, 140–159 mm Hg, 160–179 mm Hg, ≤180 mm Hg, ≤220 mm Hg, and an individualized group. A survey investigating the current application of the 2018 AHA/ASA guidelines for BP management after MT found that most institutions (91%) would only individually target post-MT SBP but not diastolic blood pressure (DBP) or mean arterial pressure (MAP). Moreover, 27.6% of institutions would aim for SBP at any value ≤180 mm Hg in patients with successful reperfusion (mTICI 2b-3), which was also recommend by the guideline, and the number increased to 43.1% if reperfusion was not achieved successfully (mTICI 0–2a); the remaining institutions would follow their own protocol.[18] The results of this survey typically reflect the inconformity between current practice and guidelines.

The recommendations on BP treatment after thrombectomy in AIS are inconsistent because it remains unclear whether BP elevation is a cause or just a poor outcome marker. Supposing that BP elevation is a marker of a poor outcome, wide ranging management is readily acceptable; however, if the reverse is true, and BP elevation is the cause of a poor outcome, more fastidious and individual management is required.

Pathophysiology
Collaterals and BP
Ischemic stroke is a dynamic process that cannot be completed in one attack; 1.9 million neurons and 1.8 days of healthy life pass away every minute in AIS if reperfusion is not reached in a timely manner.[19,20] Ischemia is characterized as cerebral blood flow (CBF)<20 mL/100 g/min, and when the blood

flow of that area drops below 10 or 12 mL/100 g/min, the infarction core begins to take shape.[21] CBF recovery is needed as soon as possible before cell death occurs and to save the penumbra. The penumbra is an ischemic ring surrounding the infarct core with the potential for recovery and is destined for cell death without reperfusion. First conceptualized through animal models in 1977 by Astrup et al,[22] the penumbra was defined as salvageable brain tissue with the threshold between electric failure and energy failure in 1981.[23] Since then, different animal models of cerebral ischemia used to determine the essential CBF of the penumbra have been developed.[24–29] With the development of imaging techniques, the penumbra was later detected by PET in animal models and humans,[30–32] while MRI and CTP have been more widely used to discriminate the penumbra in clinical practice due to the advantages of rapid diagnosis and easy acquisition.

The penumbra is still salvageable mainly owing to collateral circulation, but the relationship between BP and collaterals has not been rigorously studied. A retrospective cohort study showed that higher arterial BP was associated with improved leptomeningeal collaterals.[33] Cerebral flow augmentation resulting from increased BP is of vital importance in protecting the penumbra before recanalization, which was demonstrated by retrospective studies showing that decreased BP during MT was associated with poor outcomes, and BP elevation is common prior to recanalization.[34–38] An ongoing RCT (NCT04218773) is attempting to confirm the positive effect of BP elevation through SBP augmentation by 20% to at least 160 mmHg until blood vessel recanalization is accomplished or MT is completed. From this point of view, it is not surprising that higher BP or even induced hypertension is acceptable before recanalization to preserve the penumbra. The post hoc analysis of the ASTER trial found that BP variation during MT correlated with poor outcomes irrespective of any collateral status.[39] For patients with successful reperfusion after MT, higher BP variability was observed to have a harmful influence on outcomes in those with poor collaterals.[40]

Cerebral Autoregulation and BP

Under normal circumstances, cerebral autoregulation (CA) plays a significant role in sustaining CBF, while arterial blood pressure (ABP) fluctuates.[41] In AIS, CA functions in preventing hyperperfusion of the penumbra. The ischemic brain is more vulnerable to changes in SBP after dysfunctional autoregulation;[42,43] hence, once CA is impaired, ABP fluctuation may do more harm to the ischemic area. The impairment of dynamic CA has been shown and reported in several studies using different assessment methods, and its duration may last

for at least one or two weeks.[44–48] When exploring the optimal BP in post-MT patients, the impact of CA must not be overlooked. In addition, considering the duration of CA impairment, meticulous BP management may be performed for at least one or two weeks.

Myogenic, neurogenic and metabolic mechanisms were all observed in CA, none of which would act alone in BP regulation. Myogenic mechanisms may be more efficient due to the rapid changes in arterial pressure in AIS.[49] A study using a murine model demonstrated that longer reperfusion was accompanied by decreased myogenic reactivity,[50] which would result in CA impairment. However, heterogeneity exists in myogenic tone between different cerebral arteries that participate in autoregulation,[51] and the exact mechanisms of autoregulation in AIS are still unclear. Several approaches are used in clinical practice for evaluating CA and demonstrating an exact linear relationship between BP and CBF, but until now, no gold standard exists for ideally assessing CA. On account of the complicated mechanisms of CA and the absence of standard assessment for CA, the first-best BP to ensure felicitous CBF is still a challenge.

Ischemic Reperfusion Injury and BP

Reperfusion treatment is complicated by ischemic reperfusion injury because blood flow restoration and reoxygenation may paradoxically aggravate damage to ischemic brain tissue. The mechanisms for ischemic reperfusion injury include processes of vascular leakage, no reflow phenomenon, cell death programs, autoimmunity, transcriptional reprogramming and innate and adaptive immune activation,[52] which may eventually impair the blood-brain barrier (BBB).[53] The subsequent clinical manifestation is brain edema and hemorrhage, from which patients may not benefit from recanalization or even undergo an aggravated process. Both edema and hemorrhage can cause additional compression, ischemia and toxicity-related injury.

Therefore, elevated BP not only improves CBF in ischemic areas but also produces excessive impairment to the brain once reperfusion is reached and the BBB is disrupted. BP management for patients after stroke thrombectomy should balance hypoperfusion and hyperperfusion. The ischemic reperfusion injury models support proper BP reduction in patients with AIS after reperfusion and indicate that simple antihypertensive treatment may be insufficient.

Influence of BP on Outcomes

Study opinions are divergent about the relationship between BP and outcomes in AIS, and a U- or J-shaped effect of BP was
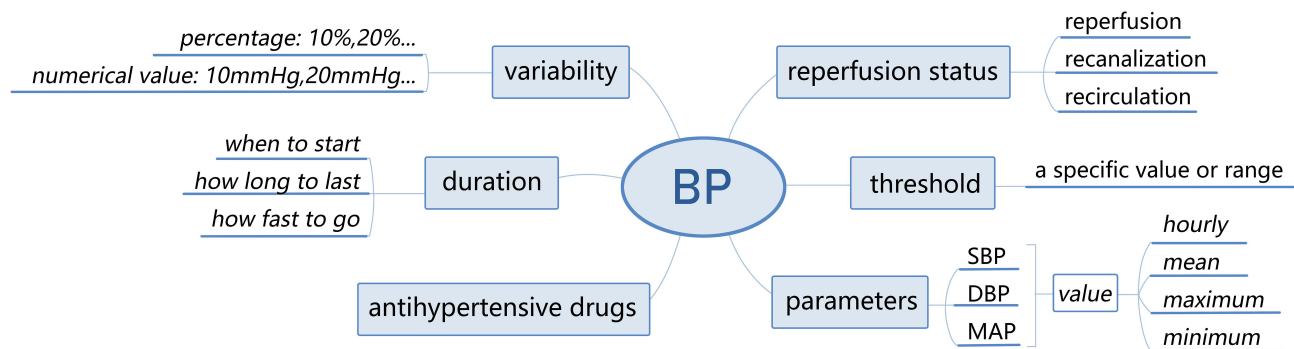
Figure 1 Several aspects of blood pressure management are to be solved after stroke thrombectomy.
Abbreviations: BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

widely discovered in retrospective studies.[13,54,55] Prior RCTs attempting to find a relationship between BP lowering and outcomes in acute strokes raised debate,[56–67] with some demonstrating promising effects of BP lowering, while others did not. These RCTs were not very comparable because most did not share the same onset time, therapeutic schedule, and type, duration and dosage of antihypertensive drugs. A meta-analysis found conspicuous heterogeneity among these studies and concluded a neutral effect of BP lowering in ischemic strokes,[68] which was not convincing enough for patients with MT. The included studies were not particular to participants treated with MT; therefore, more precise subgrouping methods surfaced according to different types of stroke, treatment methods and stages.

Elevated BP before and during MT is universally considered to be appropriate even without powerful evidence, and hypotension was shown to be connected with poor outcomes in some retrospective studies,[34–38] but in regard to post-MT BP management, clinical decision making may be more complex. No completed clinical RCT exists to guide BP management after MT. A randomized trial using murine models demonstrated the favorable effect of BP lowering after recanalization,[69] while a post hoc analysis of the SIESTA trial found no correlation between BP lowering and short- or long-term functional outcomes.[70] Moreover, in line with some retrospective studies that found that hypertension is associated with worse outcomes,[71–75] elevated BP after MT may need to be lowered. All of these studies are not BP-based interventional studies; RCTs are needed, and more attention should be paid to several aspects as follows when exploring the influence of BP on patient outcomes after MT (Figure 1).

Reperfusion Status

Once thrombectomy is completed, regardless of whether reperfusion is reached, the postthrombectomy period begins. During this period, recanalization status has an immense effect on BP after MT. John et al found that SBP may drop spontaneously after MT irrespective of the recanalization status, and in patients with unsuccessful recanalization, SBP may decrease more slightly but eventually arrive at levels similar to patients after successful recanalization within 24 h.[76] Martins et al discovered a linear relationship between SBP and functional outcome in recanalized patients, in which higher SBP was correlated with poor outcomes, while in unsuccessful recanalized patients, the association was J-shaped.[77] In contrast, another study with a larger sample size proposed a linear model to better determine the relevance between functional outcome and SBP for unsuccessfully recanalized patients.[78] Ignoring the exact model, it was widely accepted that higher SBP was associated with poor outcomes in patients with successful recanalization;[79] in patients with unsuccessful recanalization, CA should increase SBP to maintain CBF for the ischemic tissue, and permissive hypertension may be more appropriate.

Successful reopening of occluded arteries (recanalization) will not always lead to complete restoration of microcirculation (reperfusion),[80–82] and reperfusion performs better in predicting the outcomes.[83] Therefore, the reperfusion status should be more significant than the recanalization status in BP management. However, recanalization is used more frequently in clinical practice, and the concept between recanalization and reperfusion is not well understood or illustrated clearly. In addition, recirculation has recently been raised again to better explain brain injury after AIS,[84] which additionally involves the venous systems, whereas the specific mechanism of recirculation is less explored. More studies are needed to better understand the effect of recanalization, reperfusion and recirculation and to further distinguish their differences regarding BP management after MT.

Threshold

Whether any optimal threshold exists for post-MT BP after reperfusion status is unclear. A prospective cohort study (BEST) reported that a peak SBP of 158 mmHg may be the best-rank threshold without adjusted analysis.[85] Goyal et al found that BP <160/90 mmHg within 24 h after MT resulted in less mortality,[71] while Ding et al indicated that SBP≤140 mmHg was related to better outcomes and lower parenchymal hemorrhage.[75] Matusevicius et al reported that 100≤SBP≤119 mmHg contributed to better functional outcomes in patients with successful recanalization, and the range was 120–139 mmHg in patients with unsuccessful recanalization.[78] Maier et al found that a maximum SBP of 159 mmHg was the best cutoff for patients with successful recanalization, while a higher SBP was associated with poor functional outcomes.[79] If any BP threshold for patients after MT exists, it may be a specific value or a range with an upper and lower cutoff based on the reperfusion status. Future studies are needed to identify the threshold to better guide practice.

Parameter

The final determination of the optimal BP threshold can never circumvent SBP, DBP and MAP, and the hourly, maximum, minimum, and mean values of each of these parameters are essential while turning point for the threshold. SBP is more adequately handled than MAP or DBP in general,[18] but whether SBP is more important than MAP or DBP remains unknown. Mistry et al demonstrated that the maximum SBP was directly associated with outcomes, while other parameters did not affect outcomes.[72] The prospective cohort study (BEST) also demonstrated the potency of maximal SBP but not DBP or MAP.[75] Moreover, Martins et al reported the usefulness of both SBP and DBP in predicting outcomes.[77] Future studies should cover all of the parameters to determine the most appropriate one.

Variability

After a BP threshold with a detailed parameter is approximately determined, we may encounter another predicament: should we control the BP to a certain point or consider BP variability (BPV)? For instance, if the target threshold of SBP is 140 mmHg, bringing a primary SBP of 180 mmHg down to this level may differ from reducing a primary SBP of 160 mmHg to this target within the same time period. A larger BPV was shown to be associated with worse outcomes in patients with AIS,[86–92] and this was also observed in the subgroup of patients with stroke thrombectomy.[40,93–95]

Clinicians may have to choose whether to reduce BP to some degree or maintain a relatively stable BP. A stable BP may be defined as fluctuation within a percentage or a detailed number, such as 10% or 10 mmHg. BP management in patients with hypertension after thrombectomy should never neglect the influence of BPV.

Duration

The next obstacle is the duration of strict BP management after MT, in which three main aspects need to be solved: start time, duration and speed. Antihypertensive treatment may start immediately after thrombectomy once patients suffer from hypertension in the intensive care unit, but during the delivery process, which primarily occurs from the catheter room to the intensive unit or, in some cases, from the catheter room to the CT or MRI room and then to the intensive room, antihypertensive treatment may not start. Furthermore, in accordance with the duration of cerebral CA impairment, particular BP management should last for at least one or two weeks;[44–48] in reality, 24 h after MT is usually evaluated and recognized as the key period in some studies,[40,71,94] and a retrospective study even found that the first 6 h was the pivotal interval.[74] Regarding speed, there is no clear recommendation on the rate of BP decline; in other words, whether BP should be reduced to a threshold intensively within minutes or dilatorily within hours is unclear.

Antihypertensive Drugs

No consensus has been reached on the best antihypertensive drug(s), and intravenous administration of drugs with quick action and short duration is universally accepted. Labetalol, hydralazine, nicardipine, clevidipine, hydralazine, enalaprilat and sodium nitroprusside are recommended by the AHA/ASA guidelines for all types of hypertension,[16] while urapidil is widely used in Europe and Asia. For patients with elevated BP after MT, the top priority may be the safety and efficacy of the antihypertensive treatment. More research is warranted to ascertain the most efficacious antihypertensive drug.

Conclusion

Elevated BP management must balance between increasing cerebral perfusion and preventing reperfusion injury. To realize this goal, a better understanding of pathophysiology is imperative. Collaterals, penumbra, infarct core, CA, preexisting hypertension and other basic statuses all need to be noted, Interactions among all these factors may influence the effect of BP on outcomes after MT, but the relationship between these factors and BP is

not well established. The unclear pathophysiology of the effect of BP on outcomes complicates the function of BP after MT. The efficacy reported in observational studies was unable to meet clinical requirements; therefore, BP-based RCTs are actively needed to provide guidance on BP management in patients after stroke thrombectomy. During the procedure, reperfusion status should be carefully considered. The threshold, parameters, variability and duration for BP and antihypertensive drugs need to be further evaluated.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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