Hemodynamics of Leptomeningeal Collaterals after Large Vessel Occlusion and Blood Pressure Management with Endovascular Treatment

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Endovascular therapy (EVT) is an effective treatment for ischemic stroke due to large vessel occlusion (LVO). Unlike intravenous thrombolysis, EVT enables visualization of the restoration of blood flow, also known as successful reperfusion in real time. However, until successful reperfusion is achieved, the survival of the ischemic brain is mainly dependent on blood flow from the leptomeningeal collaterals (LMC). It plays a critical role in maintaining tissue perfusion after LVO via pre-existing channels between the arborizing pial small arteries or arterioles overlying the cerebral hemispheres. In the ischemic territory where the physiologic cerebral autoregulation is impaired and the pial arteries are maximally dilated within their capacity, the direction and amount of LMC perfusion rely on the systemic perfusion, which can be estimated by measuring blood pressure (BP). After the EVT procedure, treatment focuses on mitigating the risk of hemorrhagic transformation, potentially via BP reduction. Thus, BP management may be a key component of acute care for patients with LVO stroke. However, the guidelines on BP management during and after EVT are limited, mostly due to the scarcity of high-level evidence on this issue. In this review, we aim to summarize the anatomical and physiological characteristics of LMC to maintain cerebral perfusion after acute LVO, along with a landscape summary of the literature on BP management in endovascular treatment. The objective of this review is to describe the mechanistic association between systemic BP and collateral perfusion after LVO and thus provide clinical and research perspectives on this topic.

Keywords Leptomeningeal collateral; Blood pressure; Large vessel occlusion; Cerebrovascular circulation; Endovascular recanalization; Ischemic stroke

Introduction

The efficacy of intravenous thrombolysis (IVT) and endovascular therapy (EVT) for acute ischemic stroke patients after large vessel occlusion (LVO) has been established by large randomized clinical trials. However, approximately 50% of patients still experience functional dependency despite successful recanalization after timely treatment. Variability in collateral perfusion before recanalization may be a potential reason for this.

The fate of brain cells in the ischemic region beyond the LVO depends on perfusion through the leptomeningeal collateral (LMC) overlying the cerebral hemisphere. Inadequate LMCs, either due to anatomical paucity or physiological dysfunction, lead to rapid infarct growth and may contribute to the pro-
Anatomy and physiology of leptomeningeal collaterals

Anatomy
In a normal physiological state, blood flows from the heart to the brain via the anterior circulation, which comprises the internal carotid artery, the middle cerebral artery (MCA), which supplies the majority of this circulation, and the anterior cerebral artery (ACA). Blood also flows via the posterior circulation, which is formed by the vertebral artery, basilar artery, and posterior cerebral artery (PCA). The average diameter of the MCA at its origin is approximately 4 mm, roughly twice that of the ACA, which is approximately 2 mm. As the amount of blood flow roughly corresponds to the vascular diameter, the average CBF in the MCA (146±31 mL/min) usually exceeds the flow in the ACA (82±18 mL/min).9

On the surface of the cerebral hemisphere, the pial arteries lie within the subarachnoid space and provide perforating arteries into the brain parenchyma. The proximal part of the perforating arteries usually consists of an endothelium surrounded by a thick basement membrane material with embedded smooth muscle cells. However, at the capillary level, the vascular wall consists of a single layer of flattened endothelial cells with a very thin basement membrane and intermittent pericytes without smooth muscle cells.10 The diameter of perforating arterioles varies by its function and location, and can range from 10 to 240 μm, with the largest one penetrating to the bottom of the sulci.11

LMC channels consist of small precapillary arterial conduits of varying sizes lying between the pial arteries and arterioles in the cerebral cortex. There are two types of precapillary links: a larger one that connects the surface pial arteries in an end-to-end manner, and a smaller one that bridges smaller perforating arterioles often near the point of cortical penetration. The diameter of these anastomoses shows a wide range (10 to 30 μm) in their resting state.11 These anastomotic channels work as the anatomical substrate of LMCs beyond an LVO.

Physiology
Perfusion through the arterial/arteriolar anastomoses described above is regulated by CA. CA is a normal physiological response that maintains constant blood flow in response to external and internal stimuli, such as changes in arterial BP between a mean arterial pressure (MAP) of 50 to 170 mm Hg.12,13 CA provides adequate regional CBF in settings of decreased systemic perfusion or increased local metabolic demand after neuronal/cellular hyperactivity. CA is regulated by a complex interplay of myogenic, neurogenic, metabolic, and endothelial mechanisms,14 all of which modulate the diameter of cerebral vessels. Vascular smooth muscle cells at the precapillary level regulate the vascular diameter through nitric oxide from endothelial cells, neurogenic substances, and cellular metabolic by-products.15-17 At the capillary level where smooth muscle cells are not found, the pericyte at the arteriolar side may contribute to vessel diameter modulation.18

As CA depends on the regulation of arteriolar diameters, the functional capacity of CA is determined by the structural and functional properties of the pial artery and arteriolar anastomoses. The normal physiological response of vasodilation to decreased perfusion pressure is altered in various pathological conditions such as aging, long-standing hypertension, and hyperglycemia.19-21 This resulting impairment in the CA response is not an all-or-none phenomenon but rather a graded and variable response (Figure 1).22,23

Leptomeningeal collateral perfusion and systemic blood pressure after large vessel occlusion
After LVO, a significant drop in local perfusion pressure occurs within the affected vascular territory, resulting in a mismatch between metabolic demand and oxygen/nutritional supply. In response to this, LMCs are recruited by vasodilation of the pial arteries and arteriolar anastomoses to their maximum available capacity. The average diameter of these anastomoses is less...
than 10 to 20 μm in the resting state, but when fully recruited after LVO, their diameter increases almost 6-fold (60 to 120 μm). Experimental animal model data have shown that this recruitment occurs almost instantaneously after LVO and takes an average of 12 seconds to reach a maximum. As the direction of blood flow through the LMC channel is determined by the perfusion pressure gradient at both ends of the conduit, the collateral perfusion passively flows from the ACA or PCA to the ischemic territory in the case of MCA occlusion.

Before successful recanalization is achieved after LVO, the objective of medical management is to prevent irreversible infarction of the ischemic penumbra. Cerebral autoregulatory mechanisms are unable to provide adequate regional CBF due to the severely depressed level of perfusion pressure, with the cardiac output now becoming the sole driving force of regional CBF. Informed by this physiological model, stroke physicians do not intentionally lower BP in acute ischemic stroke patients unless it is extremely high. However, this simple physiological model does not fully consider the complex interplay between any remaining CA capacity, extent and amount of LMC perfusion, and systemic BP. In this sense, early infarct growth will be a function of time from onset, ischemic severity, that is, baseline LMC perfusion, and tissue vulnerability.

After successful recanalization, the objective of BP management should be to mitigate the risk of hemorrhagic transformation. The prevailing belief is that lowering BP may prevent hemorrhagic transformation after EVT. However, this simple model does not consider the fact that angiographic recanalization does not always guarantee tissue reperfusion. Examples of such physiology include the “no-reflow” phenomenon and partial recanalization, situations in which patients may benefit from relatively higher local perfusion pressure.

Levels and variabilities of blood pressure in peri-endovascular treatment and stroke outcomes

In the early EVT era, studies mainly focused on one parameter for BP management: BP at the time of hospital arrival (Table 1). Both extremely high and low values of BP on arrival were associated with poor functional recovery or hemorrhagic transformation after EVT. The largest dataset to date on this topic was from the Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands (MR CLEAN) registry with 3,180 EVT cases, which showed a J-shaped association between BP on admission and
mortality or functional recovery and an inflection point at 150/81 mm Hg.\(^ \text{36} \) However, BP at presentation is not modifiable.

The effect of procedural BP during EVT is mostly analyzed in conjunction with the type of anesthesia; therefore, the BP profile in such reports cannot be entirely distinguished from its influence (Table 2).\(^ \text{40,43-61} \) It is not uncommon during general anesthesia (GA) to have hypertensive episodes due to anesthesia drugs, intravascular hypovolemia, high intrathoracic pressures, and impaired sympathetic tone.\(^ \text{62} \) GA is usually correlated with lower BP levels and unfavorable outcomes compared to local anesthesia or conscious sedation.\(^ \text{43,44} \) The Sedation vs. Intubation for Endovascular Stroke Treatment (SIESTA) and General or Local Anesthesia in Intra-arterial Therapy (GOLIATH) trials were conducted to investigate the association between anesthesia and EVT outcomes.\(^ \text{63,64} \) Post hoc analyses of these trials reported that stroke outcomes were not associated with the magnitude of BP reduction and type of anesthesia.\(^ \text{40,45} \) However, subsequent analyses showed that the degree of systolic blood pressure (SBP) or MAP reduction correlated with the volume of infarction and with clinical deficits.\(^ \text{46-48} \) When individual patient data were combined, longer cumulative durations of MAP less than 70 mm Hg or greater than 90 mm Hg were related to poor functional outcomes.\(^ \text{63} \) Likewise, data from the MR CLEAN registry showed that a combination of prolonged duration of BP reduction with lower BP level was associated with worse 3-month outcomes.\(^ \text{65} \)

BP measurements obtained after EVT received more attention only after the effectiveness of EVT was proven in clinical trials (Table 3).\(^ \text{40,65-96} \) Studies have shown that higher BP after EVT correlates with a higher risk of hemorrhagic transformation, poor functional recovery, and mortality.\(^ \text{65-69,96} \) The Blood Pressure after Endovascular Therapy for Ischemic Stroke (BEST) study, a multicenter study of 485 EVT cases collected from 12 comprehensive stroke centers, documented that peak SBP <158 mm Hg 24 hours post-EVT was associated with an increased probability of good functional outcomes.\(^ \text{70} \)

Due to the relatively regular interval of BP measurements during the post-EVT phase, the effect of BP variability post-EVT has also been investigated well, with multiple studies showing

**Table 1. Admission BP and EVT outcomes**

| Study                        | Year | Study subjects                              | Major BP indices                  | Major findings                                                                 |
|------------------------------|------|---------------------------------------------|-----------------------------------|--------------------------------------------------------------------------------|
| Nogueira et al.\(^ \text{36} \) | 2009 | 305 LVO patients included in the MERCI and multi-MERCI trials | BP on admission                    | Higher SBP on admission associated with unfavorable outcomes but an independent predictor of successful recanalization |
| Maier et al.\(^ \text{38} \)    | 2017 | 1,042 LVO patients with EVT from ETIS registry | BP on admission                    | Admission SBP showed J- or U-shaped association with mortality, with the inflection point at SBP 157 mm Hg          |
| Mulder et al.\(^ \text{37} \)   | 2017 | 500 LVO patients included in the MR CLEAN trial | BP at baseline, before EVT (for EVT group) or stroke unit admission (for the no-EVT group) | Baseline SBP showed U-shape association with functional outcome High SBP associated with mortality and symptomatic hemorrhage No interaction between SBP level and EVT |
| Goyal et al.\(^ \text{31} \)    | 2017 | 116 LVO patients with EVT                   | SBP on admission                   | Admission SBP correlated with final infarct volume Higher admission SBP associated with mRS 0–2                          |
| Schonenberger et al.\(^ \text{40} \) | 2018 | 150 EVT cases randomized to GA or CS from the SIESTA trial | BP measurements were divided into 4 phases: pre-EVT, pre-recanalization, post-recanalization, and post-EVT | No association between the difference in SBP, DBP, and MAP from baseline to the different phases of intervention with 24-hour NIHSS No association of BP drop with a change in mRS |
| Anadani et al.\(^ \text{42} \)  | 2020 | 381 EVT cases from the ASTER trial           | Baseline BP prior to randomization | No association between admission BP with mRS or successful revascularization                                            |
| van den Berg et al.\(^ \text{39} \) | 2020 | 3180 EVT patients from the MR CLEAN registry | BP on admission                    | J-shaped association with mRS and mortality with inflection points at 150 and 81 mm Hg Higher SBP associated with poor mRS and mortality |

BP, blood pressure; EVT, endovascular treatment; LVO, large vessel occlusion; MERCI, Mechanical Embolus Removal in Cerebral Ischemia Trial; Multi-MERCI, Multi Mechanical Embolus Removal in Cerebral Ischemia Trial; SBP, systolic blood pressure; ETIS, endovascular treatment in ischemic stroke follow-up evaluation study; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands; mRS, modified Rankin Scale; GA, general anesthesia; CS, conscious sedation; SIESTA, Sedation vs. Intubation for Endovascular Stroke Treatment trial; DBP, diastolic blood pressure; MAP, mean arterial pressure; NIHSS, National Institutes of Health Stroke Scale; ASTER, Contact Aspiration vs. Stent Retriever For Successful Revascularization trial.

*This article covers all peri-EVT periods.*

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### Table 2. BP during the EVT procedure and outcomes

| Study                                      | Year | Study subjects                                                                 | Major BP indices                                                                 | Major findings                                                                 |
|--------------------------------------------|------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| Davis et al.                               | 2012 | 96 EVT cases (48 GA and 48 LA)                                                  | SBP, DBP, and MAP (minimum and maximum values for each) in LA and GA groups     | Higher rates of mRS 0–2 in LA groups; lower SBP levels in GA group            |
| Hendén et al.                              | 2015 | 108 EVT cases                                                                  | Fall in MAP of >40% compared to the baseline under GA                            | Fall in MAP of >40% from baseline associated with poor neurological recovery |
| John et al.                                | 2015 | 147 EVT during 2008–2012                                                        | Levels of BP during the EVT procedure under GA                                   | Lower maximum intraprocedural SBP associated with mRS 0–2                     |
| Jagani et al.                              | 2016 | 99 EVT with CS or GA                                                            | Maximum or minimum values of SBP, DBP, and MAP                                   | GA associated with lower BP levels and poor outcome                           |
| Whalin et al.                              | 2017 | 255 Anterior circulation occlusions with mTICI ≥2b with monitored anesthesia care | MAP level during the procedure with monitored anesthesia care                    | 10% MAP drop associated with poor functional outcome                         |
| Athiraman et al.                           | 2018 | 88 EVTs under GA                                                                | Episodes or durations of SBP lower than specific thresholds                     | Lower SBP levels associated with poor outcome                                 |
| Pikija et al.                              | 2018 | 164 EVT cases under GA                                                           | In-procedure SBP and MAP excursions to >120%/80% of the reference value and the reference BP/weighted in-procedure mean BP | Higher in-procedure SBP/MAP excursion to >120% associated with lower infarct volume and mRS 0–2; Higher in-procedure mean SBP/MAP associated with lower rates of hemorrhage |
| Rasmussen et al.                           | 2018 | 128 EVT patients randomized to GA or CS from the GOLIATH trial                  | Levels and durations of SBP or MAP lower than specific thresholds               | Higher MAP or SBP levels in CS group                                           |
| Schonenberger et al.                       | 2018 | 150 EVT cases randomized to GA or CS from the SIESTA trial                      | BP measurements were divided into 4 phases: pre-EVT, pre-recanalization, post-recanalization, and post-EVT | No association between the difference in SBP, DBP, and MAP from baseline to the different phases of intervention with 24 hours NIHSS; No association of BP drop (magnitude of changes) with a change in mRS |
| Treurniet et al.                           | 2018 | 60 EVT under GA in the MR CLEAN trial                                           | Levels and changes of SBP, DBP, and MAP during the procedure                    | Greater MAP reduction associated with worse functional outcome               |
| Petersen et al.                            | 2019 | 390 EVTs from two comprehensive stroke centers                                 | Intraprocedural MAP, delta MAP (baseline MAP–lowest MAP during EVT procedures before recanalization) | MAP reduction noted in 87% of cases during EVT; Delta–MAP associated with infarct growth and infarct volume; Delta–MAP correlated with higher mRS at discharge    |
| Pikija et al.                              | 2019 | 39 BAO with EVT                                                                 | BP levels and variability indices; difference of peak and trough values, SD, CV, ARV; reference SBP calculated as a median of the first five procedural measurements | Shorter procedural duration of SBP <140 associated with successful recanalization; Higher SBP and longer duration of SBP over 180 mm Hg associated with hemorrhage |
| Fandler-Hofler et al.                      | 2020 | 115 Anterior circulation occlusion patients with EVT under GA                  | Peri-interventional BP levels and reduction                                     | Single BP drop associated with poor outcome                                   |
| Maier et al.                               | 2020 | 381 Patients from the ASTER trial                                               | Dynamic BP parameter, CV; steady BP parameter, hypotension time of SBP <140 or MAP <90 | BP variability parameter associated with poor outcomes regardless of collateral status; Hypotension time associated with poor outcomes only in patients with poor collaterals |
| Petersen et al.                            | 2020 | 90 EVTs for anterior circulation occlusions                                    | Optimal ranges of MAP based on an autoregulatory index calculated by a real-time NIRS in response to changes in MAP | Percent time of MAP greater than the upper limit of the optimal range associated with worse 90-day outcomes and trends in hemorrhage |
| Rasmussen et al.                           | 2020 | 368 EVT patient’s data from SIESTA, ANSTROKE, GOLIATH trials (CS vs. GA)        | Levels and durations of MAP greater or less than thresholds                     | Cumulative hypotension (MABP <70 mm Hg for >10 minutes) and hypertension (MABP >90 mm Hg for >45 minutes) associated with poor functional outcomes |
| Valent et al.                              | 2020 | 371 EVT cases under GA or CS                                                    | Baseline BP; BP measured in the interventional suite immediately before the induction Duration of arterial hypotension (below the baseline BP) | The time below 90% of the reference value associated with mRS ≥3 |

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Table 2. Continued

| Study                                      | Year | Study subjects                                      | Major BP indices                                             | Major findings                                                                 |
|--------------------------------------------|------|-----------------------------------------------------|--------------------------------------------------------------|--------------------------------------------------------------------------------|
| Samuels et al. [40]                        | 2021 | 440 EVT patients from the MR CLEAN registry, under CS or LA | Changes and duration of MAP levels                            | Lower MAP levels in CS; worse outcome in CS                                      |
| Xu et al. [42]                             | 2021 | 131 EVT patients after LVO under GA                 | Delta MAP; MAP every 5 minutes–baseline MAP                   | Longer duration delta MAP associated with poor outcome, but only documented in mild reduction group |
| Chen et al. [61]                           | 2021 | 139 EVT cases with successful recanalization       | Procedural BPs categorized into baseline, pre-recanalization, post-recanalization, and post-intervention | High pre-recanalization BPs associated with poor outcomes; protocol-based BP lowering during EVT not associated with outcomes |

BP, blood pressure; EVT, endovascular treatment; GA, general anesthesia; LA, local anesthesia; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; mRS, modified Rankin Scale; CS, conscious sedation; mTICI, modified treatment in cerebral ischemia; GBAUATH, General or Local Anesthesia in Intra-arterial Therapy trial; SIESTA, Sedation vs. Intubation for Endovascular Stroke Treatment trial; NIHSS, National Institutes of Health Stroke Scale; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in the Netherlands; BAQ, basilar artery occlusion; SD, standard deviation; CV, coefficient of variation; ARV, average real variation; ASTER, Contact Aspiration vs. Stent Retriever For Successful Revascularization trial; NIRS, near-infrared spectroscopy; ANSTROKE, Anesthesia During Stroke trial; MABP, mean arterial blood pressure; LVO, large vessel occlusion.

*This article covers all peri-EVT periods.

Table 3. Post-procedural BP and the recanalization treatment outcomes

| Study                                      | Year | Study subjects                                      | Major BP indices                                             | Major findings                                                                 |
|--------------------------------------------|------|-----------------------------------------------------|--------------------------------------------------------------|--------------------------------------------------------------------------------|
| Martins et al. [71]                       | 2016 | 674 IVT or EVT cases                               | BP every 2 hours for 24 hours after admission                | SBP showed J-shape in non-recanalized group but linear association in recanalized group |
| Mistry et al. [80]                        | 2017 | 228 EVT from three hospitals                       | BP (max, min, and average) in the first 24 hours after EVT   | High peak SBP correlated with worse functional outcome and hemorrhagic complications |
| Goyal et al. [86]                         | 2017 | 217 LVO with EVT with hourly BP                    | BP goals post EVT; permissive hypertension (<220 or 185), moderate BP control (<160), intensive BP control (<140) | Higher SBPmax associated with mortality Intensive BP target (<140/90 mm Hg) associated with higher rates of mRS 0–2 |
| Bennett et al. [70]                       | 2018 | 182 LVO patients with EVT                          | Post-procedural BP variability indices; SD, CV, and SV       | High BPV associated with high mRS                                                   |
| Chang et al. [81]                         | 2018 | 303 LVO patients with EVT                          | Post-procedural BP variability indices; SD, CV, and VIM      | High BPV associated with poor functional recovery and low successful recanalization |
| Maier et al. [82]                         | 2018 | 168 Anterior circulation occlusions with successful recanalization after EVT | Mean, max, and peak SBP for the first 24 hours after successful EVT | High mean SBP and maximum SBP associated with unfavorable outcome |
| Martins et al. [80]                       | 2018 | 674 IVT or EVT                                      | Standard deviations of SBP and DBP during the first 24 hours after stroke | A differential effect from SD of SBP on mRS by recanalization status; significant only in non-recanalized patients |
| Schonenberger et al. [89a]                | 2018 | 150 EVT cases randomized to GA or CS from the SIESTA trial | BP measurements were divided into 4 phases: pre-EVT, pre-recanalization, post-recanalization, and post-EVT | No association between the difference in SBP, DBP, and MAP from baseline to the different phases of intervention and NIHSS change after 24 hours No association of BP drops with a change in mRS |
| Cernik et al. [65]                        | 2019 | 690 EVT patients                                   | Levels of SBP and DBP                                        | Low BP levels associated with better functional recovery or recanalization        |
| Chang et al. [82]                         | 2019 | 90 EVT with mTICI ≥2b                               | BP variability indices                                       | BP variability associated with poor mRS only in patients with poor collaterals at baseline |
| Cho et al. [84]                           | 2019 | 378 EVTs                                           | Levels and variability indices during the first 24 hours after admission | Higher mean SBP and SV of SBP associated with poor mRS; the effect of SV modified by recanalization status |
| Choi et al. [85]                          | 2019 | 1,540 AIS patients after IVT or EVT                 | BP ≤130/80 mm Hg                                              | Lower BP levels associated with mRS 0–2                                            |
| Kim et al. [71]                           | 2019 | 211 EVT with mTICI ≥2b                              | Levels, excursions, variability indices, and time rate of BP variation | BP variability indices associated with higher rates of SICH                        |
| Mistry et al. [70]                        | 2019 | 485 Consecutive EVT patients from 12 centers        | All SBP values within 24 hours post EVT                      | Peak SBP <158 mm Hg associated with good functional outcome Overall, SBP showed a U-shape association with outcome Higher BP levels after EVT associated with poor outcome |
Table 3. Continued

| Study | Year | Study subjects | Major BP indices | Major findings |
|-------|------|----------------|------------------|---------------|
| Zhang et al. 56 | 2019 | 72 LVOs with EVT | Post-procedural BP variability indices; SD, CV, and SV | Higher SV of SBP correlated with mRS at 3 months |
| Anadani et al. 57 | 2020 | 1,361 EVT cases from an international multicenter study | SBP reduction in the first 24 hours after EVT | SBP reduction associated with a good outcome only in patients with complete reperfusion (mTICI, 3) |
| Anadani et al. 58 | 2020 | 433 EVT cases from the BEST study 59 | SBP reduction, the absolute difference between admission SBP and mean SBP in the first 24 hours | No association between SBP with poor outcome or death |
| Anadani et al. 60 | 2020 | 1,019 Anterior circulation occlusion patients with EVT from eight comprehensive stroke centers | Post-EVT BP target, <140, <160, and <180 | Lower SBP goal (<140 or <160, compared to <180) associated with good outcome However, mean achieved SBP levels tended to overlap |
| Cheng et al. 61 | 2020 | 124 Anterior circulation occlusion patients with EVT | Two BP measurements immediately after successful recanalization | Higher BP associated with PH2 hemorrhagic transformation |
| Chu et al. 62 | 2019 | 166 EVT patients | Hourly BP after EVT, by 1–6, 7–12, 13–18, and 19–24 hours | Lower mean, max, SD of SBP, and DBP associated with functional independence, in <6 hours |
| Dias et al. 63 | 2020 | 458 EVT cases | Median SBP within the first hour after EVT | Lower median SBP associated with NIHSS reduction by 8 or ≤2 at 24 hours |
| Ding et al. 64 | 2020 | 262 EVT cases | Maximum SBP and DBP for 24 hours after the EVT | Max SBP associated with poor mRS and parenchymal hemorrhage (hyper attenuated lesion on immediate CT, cannot distinguish from contrast staining) |
| Matsuvecius et al. 65 | 2020 | 3,631 EVT cases from the SITS-ISTR registry | Mean 24-hour SBP after EVT | Higher SBP associated with poor functional recovery in successful recanalization patients and with SICH in all recanalization |
| McCarthy et al. 66 | 2020 | 212 EVT patients | Daily peak SBP and DBP | Higher peak 24-hour SBP associated with SICH and poor outcome Higher peak SBP at day 2 and day 3 associated with poor outcome |
| Mistry et al. 67 | 2020 | 443 EVT cases from the BEST study 68 | Systolic BPV (SD, CV, ARV, SV, and rSD) during 24 hours after EVT | Higher BP variability associated with poor outcome and mortality |
| Anadani et al. 69 | 2021 | 5,835 EVT patients from the SITS-ISTR registry | Delta SBP (SBP–baseline SBP) 0–2/2–4/4–12/12–24 hours | SBP elevation after EVT associated with poor functional outcome |
| Gigliotti et al. 70 | 2021 | 117 EVT cases | SBP for 24 hours after EVT | SBP ≥180 associated with poor function at discharge but not at 3 months SBP ≥160 associated with malignant cerebral edema with lower symptomatic hemorrhage |
| Han et al. 71 | 2021 | 187 BAO with EVT | Levels of SBP, MAP, and DBP | Maximum SBP and maximum MAP associated with mortality |
| Huang et al. 72 | 2021 | 502 Anterior circulation LVO patients with EVT | Levels and variability indices of SBP and DBP | High BP variability associated with poor functional recovery and hemorrhagic complications, differentiated by recanalization status, not by baseline collaterals |
| Liu et al. 73 | 2021 | 596 LVO patients with EVT (GA in 37%) | BP for 24 hours after EVT | Higher mean SBP levels, mean SBP >140, and SD of SBP associated with the unfavorable outcome only in poor collaterals subgroup |
| Mazighi et al. 74 | 2021 | 324 LVO patients with EVT (BP-TARGET trial) | Randomized to intensive SBP target (100–129) vs. standard SBP target (130–185) for 24 hours | No difference in the primary outcome (any hemorrhage or hypotensive event) |
| Castro et al. 75 | 2021 | 146 Anterior circulation LVO with successful recanalization | Spectral analysis of 5-minute recordings of beat-to-beat BP | High frequency BP variability associated with cerebral edema and unfavorable functional outcomes |

BP, blood pressure; IVT, intravenous thrombolysis; EVT, endovascular treatment; SBP, systolic blood pressure; LVO, large vessel occlusion; mRS, modified Rankin Scale; SD, standard deviation; CV, coefficient of variation; SV, successive variation; BPV, BP variability; VIM, variation independent of the mean; GA, general anesthesia; CS, conscious sedation; SIESTA, Sedation vs. Intubation for Endovascular Stroke Treatment trial; DBP, diastolic blood pressure; MAP, mean arterial pressure; NIHSS, National Institutes of Health Stroke Scale; mTICI, modified treatment in cerebral ischemia; AIS, acute ischemic stroke; SICH, symptomatic intracranial hemorrhage; BEST, Blood Pressure after Endovascular Therapy for Ischemic Stroke study; CT, computed tomography; PH2, parenchymal hemorrhage type 2; SITS-ISTR, Safe Implementation of Thrombolysis in Stroke International Stroke Thrombolysis Registry; ARV, average real variation; rSD, residual standard deviation; BAO, basilar artery occlusion; BP-TARGET, Blood Pressure target in Acute Stroke to Reduce Hemorrhage after Endovascular Therapy trial.

*This article covers all peri-EVT periods.
that higher BP variability is associated with larger infarct volume and poor functional recovery.\textsuperscript{70,71} In a secondary analysis of the BEST study, it was shown that the correlation between BP levels and poor functional outcomes became more robust in the group with high BP variability, which suggests an additive effect of BP variability over absolute BP levels.\textsuperscript{72} One shortcoming of such analyses is the neglect of the time gap between BP measurements when measuring BP variability. To address this issue, the concept of the rate of BP change, that is, mm Hg/min, was proposed. This rate of change in BP was associated with an increased risk of symptomatic hemorrhage after EVT in one study.\textsuperscript{73} Spontaneous reduction of BP after recanalization is well known.\textsuperscript{74} In the post-EVT phase, some studies have noted poor outcomes with less BP reduction in those who had relatively higher BP compared to the baseline.\textsuperscript{70,71} Current analyses of BP variability, however, continue to be limited. Future analyses may need to incorporate longer-term trajectories and the rapidity of changes in BP readings during the hyperacute period.

**Summary of current evidence for clinical practice**

Current clinical guidelines and summary of the literature on BP management during the peri-endovascular treatment period

The BP management recommendations from current guidelines may be summarized as follows:\textsuperscript{28,29}

1. Routine use of BP-lowering medication before recanalization treatment (thrombolysis and/or EVT) is not well established and is not recommended unless >220/110 mm Hg.
2. For IVT alone, it is recommended to maintain a BP <185/110 mm Hg before, during, and 24 hours after treatment.
3. For EVT, intensive BP lowering in the peri-EVT period lacks clear benefits. It is suggested that BP be maintained at <185/105 mm Hg during and after the procedure. This recommendation was based on recent clinical trial protocols.

The landscape review from the previous section can be summarized as follows:

1. Admission BP has a J- or U-shaped association with clinical outcomes after EVT.
2. Prolonged duration of low BP during EVT procedures is associated with unfavorable outcomes.
3. BP variability after EVT correlates with a higher risk of poor functional recovery and/or increased rates of hemorrhagic complications.
4. Relatively lower BP reductions after EVT are associated with poor functional recovery.

**A tentative suggestion for the BP management of patients with EVT**

**Pre-EVT period**

The objective of BP management during this period should be to maximize the viability of the ischemic penumbra. The recent literature is inconclusive, with both higher or lower levels of admission BPs reported to be correlated with poor outcomes. Current guidelines recommend that EVT candidates maintain an SBP <185 mm Hg. This BP threshold is a legacy from the eligibility criteria for the intravenous thrombolysis trial.\textsuperscript{75} Although this threshold BP level was not validated in any of the EVT trials, there is currently no evidence to suggest any other threshold level in these patients. Likewise, there is still minimal evidence to support increased cerebral perfusion after an LVO stroke after iatrogenically induced hypertension. Thus, it is advisable to maintain the BP level that the patient presents before the initiation of EVT.

**Procedural BP**

Most studies investigating procedural BP levels reported a higher likelihood of poor outcomes after a prolonged duration of lower or higher BP. However, these two points require further discussion. First, these were post hoc analyses of studies that compared the route of anesthesia. Thus, the deleterious effect of low BP cannot be separated from that of anesthetic.\textsuperscript{48-50} Second, collateral perfusion through the LMC mainly works before recanalization. The collateral perfusion will instantaneously reverse back to physiological status as soon as the orthotropic flow is restored.\textsuperscript{5} Therefore, the procedural BP management strategy may need to distinguish whether recanalization is achieved.

Before recanalization, as in the pre-EVT period, the objective of BP management should be to ensure the viability of the ischemic penumbra. Prolonged exposure to low or high BP should be avoided. A mean arterial BP range between 70 and 90 mm Hg was suggested by one study.\textsuperscript{49} After recanalization, the BP management strategy would follow that for the post-recanalization period.

**Post-recanalization period**

The primary goal of BP management after successful recanalization is to mitigate the risk of hemorrhagic complications and stabilize ischemic tissues. Randomized clinical trials to test the efficacy of EVT for anterior circulation LVO have specified some BP management instructions. The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial recommended SBP values ≥150 mm Hg.
while the artery remains occluded; controlling BP once reperfusion has been achieved while aiming for a normal BP in an individual is sensible. A recent EVT trial proposed SBP <140 mm Hg after successful EVT. In general, higher BP levels during the acute period tend to stabilize after recanalization treatment. Post hoc analyses of the BEST study and the Safe Implementation of Thrombolysis in Stroke International Stroke Thrombolysis Registry (SITS-ISTR) identified that higher BP after EVT is associated with poor outcomes. Further studies and discussion should be conducted to investigate whether the unfavorable effect of higher-than-usual BP is reproduced consistently over the recanalization grades, that is, cases with post-EVT recanalization grades modified treatment in cerebral ischemia (mTICI) 2b, 2c, and 3. A patient who had mTICI of 2b recanalization but with occlusion of a distal branch supplying the precentral gyrus may benefit from higher BP levels to support local LMC perfusion. Additionally, the association between BP variability and poor treatment outcomes has been consistently reported in the post-EVT period. Lastly, there is limited evidence that higher BP levels after recanalization cause hemorrhagic transformation.

Thus, the following rule of thumb may be considered until more evidence emerges.

1. In the post-recanalization period, it is best to maintain the BP level of the patient.
2. The practice of lowering SBP to less than 140 mm Hg after successful recanalization is not based on proven evidence.
3. We suggest monitoring BP levels after recanalization and treating only if BP levels are very high; for example, >185 mm Hg systolic when IVT has already been offered or when recanalization grade mTICI 2c or 3 has been achieved.
4. Higher BP levels after recanalization may portend unfavorable treatment outcomes.

Research perspective

Despite a large body of literature, current clinical guidelines provide limited recommendations regarding BP management strategies in the peri-EVT period. One obvious reason is the retrospective and observational design of published studies. However, BP can be easily measured and readily controlled by parenteral medications. Owing to constant fluctuation in BP during this period, clinical inertia, that is, ignoring outlier BP values, may creep unintentionally. The discrepancy between a prespecified BP target and achieved BP levels is not infrequent in real-world clinical practice. In a recent clinical trial, the BP-Blood Pressure target in Acute Stroke to Reduce Hemorrhage after Endovascular Therapy (TARGET) study randomized 324 cases into an intensive SBP target (100 to 129 mm Hg) and a standard SBP target (130 to 185 mm Hg) during the 24 hours after EVT. The two groups were comparable in radiographic intraparenchymal hemorrhage at 24 to 36 hours, as well as functional recovery and safety outcomes. However, there was an unintended crossover between the assigned target group; patients in the intensive arm spent approximately a third of the duration in the SBP target range of the control arm. Such crossover was also noted in a prospective cohort from eight comprehensive stroke centers that grouped EVT patients into intensive (<140 mm Hg), moderate (<160 mm Hg), and usual (<180 mm Hg) SBP management groups. Despite significant benefits from the moderate target compared to the guideline-recommended target group, the mean SBP levels were almost identical in both groups. Studies focusing on prespecified SBP targeting after EVT need to consider the stabilizing trends of BP after treatment and the inadvertent effect of treating physicians’ behavior and preconceptions.

Summary measures for BP

Repeated measures of BP over time were obtained from a single patient. However, in clinical practice, these measurements are recorded over various time intervals, thus providing only a screenshot of the dynamic readings in time. Considering that every cardiac beat generates SBP and diastolic BP (Figure 2A), the recorded BP values represent only a fraction of the potentially available BP data. Therefore, to capture maximum information, researchers need to carefully choose indices such as BP level, BP variability, and BP trajectory (Figure 2).

BP level, usually presented as mean BP over a specific duration, expresses the status of BP at a particular time point or period. This level is intuitive to physicians, and the change in the BP level may provide practical information (Figure 2B). However, this measure does not capture information about the BP variation generated by every cardiac beat. Variability is a summary measure of the fluctuation of the measurements over a specific duration (Figure 2C). It is not easy to set up a specific threshold of BP variability that warrants clinical intervention, as accurately measuring variability requires a sufficient count of BP measurements to be calculated. It should also be acknowledged that variability indices are affected by the temporal density of BP measurements and BP levels. The absolute BP variability value may decrease during a high measurement density period, that is, during the EVT procedure. Short-term variability is also affected by physical activity, emotional stress, and circadian rhythm, all of which augment the complexity of interpretation of such data. BP trajectories focus on identifying a specific group following a similar trend and pattern of...
The relationship between leptomeningeal collaterals and blood pressure in patients with large vessel occlusions

As discussed in this review, regional tissue perfusion after LVO is maintained by the LMC channels. The recruitment of these LMC channels is determined by the pressure gradient between the arterial blood flow generated by cardiac contraction and venous blood flow. Based on this simple and linear model, it is intuitive to suppose that cerebral tissue perfusion after LVO may be regulated through systemic BP management.

However, the small arteries and arterioles of the brain have CA capacity, which modulates the vascular diameter to maintain almost constant CBF in response to local perfusion pressure changes. Therefore, the brain tissue that may receive increased local CBF from augmenting systemic BP is likely to be either the ischemic core or the ischemic penumbra without autoregulatory function. A long history of hypertension may indicate impaired autoregulatory function. Additionally, as the blood flow inversely corresponds to the fourth-order of the vascular luminal diameter, the LMC perfusion will not suffice to replace the normal physiologic CBF through anatomically intact large vessels.

Based on the above, the following can be stated:
(1) The effect of systemic BP on blood flow distal to an LVO may vary based on the anatomic extent of the LMC channels and the remaining autoregulatory function.

(2) Ischemic brain injury may affect the vascular endothelium, pericytes, glia, and neuronal cells, and it prevents the maintenance of normal autoregulatory function. The autoregulatory function may also be affected by prior conditions, such as hypertension and diabetes mellitus.

(3) In general, LMC perfusion only provides inadequate blood flow that cannot sustain brain tissue viability for long.

(4) The BP management strategy for acute ischemic stroke patients may need to be personalized based on the individual assessment of the LMC channels and autoregulatory capacity.

Whether baseline hemodynamic status modifies the association between BP profiles and ischemic or functional outcomes is a fascinating research topic. This issue has recently gained interest with studies showing that poor baseline collaterals can aggravate the deleterious effects of higher BP levels or higher BP variability on clinical outcomes. The association between BP and stroke outcomes may also differ by baseline perfusion status, that is, the extent and grade of LMC and tissue perfusion. As discussed in the previous section, early infarct growth may be a function of time from onset, ischemic severity (i.e., baseline LMC perfusion), and tissue vulnerability. It can be speculated that in patients with poor LMCs after LVO, ischemic injury rapidly develops, and the only effective treatment strategy is to expedite recanalization. In contrast, in the presence of moderate LMCs, tissue viability mainly depends on systemic perfusion, and clinicians should be sensitive to even minute changes in BP. Meanwhile, in patients with excellent or good collaterals, one can expect a higher tolerance to modest BP fluctuations. This conjecture needs to be validated in future studies.

Conclusions

In current practice, stroke physicians use BP measurements as a proxy for brain perfusion pressure. Conceptually, the objective of BP management in the pre-recanalization phase is to maintain sufficient LMC perfusion. In the post-recanalization phase, the objective is to prevent hemorrhagic complications and stabilize the ischemic brain tissues. At present, the available research on BP management in EVT shows that higher BP on admission, lower BP levels post-recanalization, higher BP variability or variable trajectories, and prolonged durations of low BP during EVT are all associated with poor functional outcomes. However, the optimal BP level, variability, and trajectory for each phase are yet to be determined. Based on current anatomical and physiological knowledge, the ultimate goal is to directly gauge the amount and capacity of LMC perfusion after LVO to provide maximally available CBF to the ischemic brain until successful recanalization is achieved and to mitigate undesirable complications subsequent to ischemia and reperfusion. Given the heterogeneity of the anatomy and variability of the physiology of the LMC, understanding its behavior during stroke is now more pressing than ever. It is paramount that more novel mechanisms and parameters to assess regional brain perfusion and functioning CA capacity at the bedside are developed in order to individualize BP management in the peri-EVT period.

Disclosure

The authors have no financial conflicts of interest.

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