



Original Contribution

Cerebrovascular risks with rapid blood pressure lowering in the absence of hypertensive emergency



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ABSTRACT

Study objective: In the Emergency Department (ED) setting, clinicians commonly treat severely elevated blood pressure (BP) despite the absence of evidence supporting this practice. We sought to determine if this rapid reduction of severely elevated BP in the ED has negative cerebrovascular effects.

Methods: This was a prospective quasi-experimental study occurring in an academic emergency department. The study was inclusive of patients with a systolic BP (SBP) > 180 mm Hg for whom the treating clinicians ordered intensive BP lowering with intravenous or short-acting oral agents. We excluded patients with clinical evidence of hypertensive emergency. We assessed cerebrovascular effects with measurements of middle cerebral artery flow velocities and any clinical neurological deterioration.

Results: There were 39 patients, predominantly African American (90%) and male (67%) and with a mean age of 50 years. The mean pre-treatment SBP was 210 ± 26 mm Hg. The mean change in SBP was -38 mm Hg (95% CI -49 to -27) mm Hg. The average change in cerebral mean flow velocity was -5 (95% CI -7 to -2) cm/s, representing a -9% (95% CI -14% to -4%) change. Two patients (5.1%, 95% CI 0.52–16.9%) had an adverse neurological event.

Conclusion: While this small cohort did not find an overall substantial change in cerebral blood flow, it demonstrated adverse cerebrovascular effects from rapid BP reduction in the emergency setting.

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1. Introduction

Severe elevations in systolic blood pressure (SBP) are common among patients in the emergency department (ED) [1–3]. Marked rises in SBP over 180 mm Hg are particularly common in urban environments and minority communities, where uncontrolled chronic hypertension is highly prevalent [4–6]. Absent evidence of hypertensive emergencies, management guidelines emphasize outpatient management for gradual BP reduction [7]. Nevertheless,

there is significant heterogeneity in management of these patients, particularly as SBP approaches 200 mm Hg or greater [1,8]. Clinicians commonly administer rapid acting antihypertensive medications to reduce BP, despite a lack of data to support this approach [3,9].

Rapid BP lowering has the potential to cause adverse cerebrovascular effects, particularly in patients with chronic, uncontrolled hypertension. Over time, these patients reset their cerebral autoregulatory limits and may be less tolerant of rapid BP normalization [10,11]. The primary objective of this study was to measure cerebrovascular change in ED patients receiving rapid blood pressure reduction. The primary outcome was change in cerebral blood flow velocity, and the secondary outcome included clinical neurological adverse events.

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2. Methods

2.1. Study design and setting

This was a prospective, quasi-experimental study of adult patients treated in an urban, single site ED. The ED is part of an 810-bed, academic teaching hospital that serves as a Level I trauma center and has an annual ED volume of approximately 99,000 patients. The study occurred from July 2014 through February 2016 and was approved by the hospital's Institutional Review Board.

2.2. Selection of participants

We recruited a non-consecutive sample of patients that presented to the ED with severely elevated BP. Patients were eligible for the study if they were adults ≥ 18 years of age with SBP > 180 mm Hg on two or more consecutive readings, they reported a history of poorly controlled chronic hypertension, and the treating clinicians planned to administer antihypertensive treatment to rapidly decrease BP. Exclusion criteria were: age < 18 years, no known or previously documented history of hypertension, clinical evidence at the time of enrollment of hypertensive emergency, administration of oral or IV antihypertensive treatment prior to enrollment, known pregnancy, and inability to provide informed consent due to encephalopathy or any other cause. Clinical evidence of hypertensive emergency included acute myocardial infarction, acute heart failure or cardiogenic pulmonary edema, aortic dissection, stroke, subarachnoid hemorrhage, or encephalopathy. Furthermore, planned treatment with a slow acting oral medication only, such as amlodipine, was an exclusion criterion. Finally, patients were excluded if they lacked temporal windows for transcranial Doppler (TCD) measurements. Approximately 10% of patients have temporal bone structure that is not amenable to TCD [12]. A study team member obtained informed consent from all participants.

2.3. Methods of measurement

Research team members collected demographic and clinical information. Blood pressure measurements for study inclusion occurred on standard automated, oscillometric devices (Philips IntelliVue MP50). Following informed consent, a research team member used 2-MHz TCD probes to capture bilateral, proximal middle cerebral artery (MCA) flow velocity measurements. We used a head-frame mount to fixate TCD probes once the optimal position and depth of insonation was determined (Spencer Technologies, Redmond, WA). Through the posterior temporal window, insonation of the MCA vessels for measurements of flow velocity (peak systolic, diastolic and mean flow velocity) has been used extensively in hypertension research as a surrogate of global cerebral blood flow [13–15]. If research team members were unable to insonate the MCA, the patient's study participation was complete, and that patient was not included in the primary analysis.

Recordings of baseline MCA flow velocity occurred for a 3–5 min period. At 60 (± 15) minutes following antihypertensive treatment, a 3–5 min period of MCA flow velocity recording was repeated. We collected BP recordings concurrent with the flow velocity measurements. No flow velocity measurements were obtained beyond these two time points. Study team members recorded further information on serious adverse events potentially due to BP treatment, such as syncope or stroke-like symptoms throughout the ED stay.

We averaged flow velocity and BP values for each period of measurement. We calculated the cerebrovascular resistance index (CVRI) as mean arterial pressure (MAP) divided by mean MCA flow velocity. We also calculated Mx, a measure of cerebral autoregulation, by calculating consecutive 20-second Pearson coefficients between the beat-to-beat MAP and MCA mean flow velocity. We averaged these coefficient values over the time period of measurement to arrive at pre- and post-treatment Mx values. A positive Mx value indicates passive dependence

of cerebral blood flow on BP (loss of cerebral autoregulation) [16]. A near-zero Mx value implies active regulation of cerebral blood flow to changes in BP. An accepted cutoff to discriminate impaired cerebral autoregulation is an Mx ≥ 0.3 [17].

This was an observation study with no study-related antihypertensive intervention. Treating clinicians administered antihypertensive therapy at their own discretion, including dose and class of medication. Administration of additional IV or oral antihypertensive medications after study-related MCA flow velocity measurements was common and also occurred at the discretion of the treating clinician.

2.4. Data analysis

The primary outcome was the change in MCA mean cerebral blood flow velocity between pre- and post-treatment measurements. A sample size calculation of 38 patients was based on 80% power to detect a 10% relative change in MCA flow velocity between baseline and post-treatment measurements, assuming alpha = 0.05. The planned analysis was inclusive of all patients that received antihypertensive treatment and completed pre- and post-treatment measurements.

The primary analysis consisted of paired Student's *t*-test between baseline and post-treatment mean flow velocity measurements. Secondary analysis included the rate of adverse neurological effects with calculation of the adjusted Wald confidence interval (CI). Further analysis also included univariate comparison of patients that had more intensive BP reduction ($\geq 25\%$ drop in MAP) versus those with more modest BP reductions. We describe continuous variables with mean and standard deviation (SD) and categorical variables with counts and percentage of total. Results include 95% CI with statistical significance designated as $p < 0.05$. We performed all analyses with SAS 9.4 (Cary, NC).

3. Results

3.1. Characteristics of study subjects

Forty-eight patients were recruited to participate and gave informed consent. We excluded 9 of these patients from analysis: 5 due to inadequate temporal windows to obtain MCA signals, 2 for never receiving antihypertensive treatment, and 2 for dropping out of the study prior to post-treatment measurements. The demographics and clinical characteristics of the remaining 39 study patients are listed in Table 1. Patients were predominantly African American (90%) and male (67%),

Table 1
Demographic and clinical characteristics.

Characteristic	Value
Age, years (SD)	50 (12)
Male, n (%)	26 (67)
Race and ethnicity, n (%)	
African American	35 (90)
Caucasian	2 (5)
Latino	2 (5)
Past medical history, n (%)	
Atrial fibrillation,	1 (3)
Congestive heart failure	4 (10)
Diabetes	8 (20)
End stage renal disease	6 (15)
Hyperlipidemia	14 (36)
Hypertension	39 (100)
Myocardial infarction	5 (13)
Peripheral arterial occlusive diseases	2 (5)
Carotid stenosis	3 (8)
Stroke	6 (15)
Tobacco use, n (%)	8 (20)

and the mean age was 50 ± 12 years. All patients had a past medical history of hypertension.

The mean pre-treatment BP values were: SBP 210 ± 26 mm Hg and MAP 149 ± 18 mm Hg. The administered antihypertensive medications were IV hydralazine, IV labetalol, oral clonidine, or IV nicardipine. Most patients were ultimately discharged home after initial evaluation and management in the ED (64%). Among those admitted, the most common admitting diagnoses were severe hypertension and hypertensive urgency (43%).

3.2. Main results

Post-antihypertensive treatment, there was an average change in SBP of -38 (95% CI -49 to -27) mm Hg and MAP of -27 (95% CI -36 to -20) mm Hg. This change represented an average 18% reduction in BP (Table 2). The average change in cerebral mean flow velocity was -5 (95% CI -7 to -2) cm/s, representing a -9% (95% CI -14% to -4%) change. Figs. 1 and 2 demonstrates the change in MAP and mean flow velocity for each subject.

There were 11 (28%) patients that had $\geq 25\%$ reduction in MAP. These patients had higher baseline SBP (228 ± 12 mm Hg) versus those with less substantial MAP reduction (203 ± 12 mm Hg). The mean reduction in MAP of this latter group was $8 \pm 6\%$. The comparative change in MCA mean flow velocity (Table 3) was not statistically greater in patients with intensive BP reduction (-6 , 95% CI -13 to 0.4 cm/s) compared to those without (-4 , 95% CI -7 to -2 cm/s). There was a more substantial decrease in CVRI in those with more intensive BP reduction (-0.86 vs. -0.12 mm Hg/cm/s, $p = 0.05$). Although the Mx value in the intensive group was 0.21 versus 0.18 in the modest reduction group, this difference was not statistically significant ($p = 0.36$).

Adverse events from BP lowering occurred in 2 patients (5%, 95% CI 1–17%). Both events occurred after TCD measurements were complete and patients received additional antihypertensive treatment. One patient had reversible stroke symptoms following an overall 54% reduction in SBP, and a second patient had reversible mental status change following a 29% reduction in SBP.

4. Discussion

We enrolled a cohort of patients with markedly elevated BP but no evidence of acute, pressure-mediated organ injury. Clinicians chose to rapidly lower BP primarily for expediency. The average rapid BP lowering was 18% and there was $<10\%$ change in cerebral blood flow, as measured by MCA flow velocity. Two patients had reversible, adverse neurological events that occurred with additional antihypertensive treatment outside the period of cerebral flow velocity monitoring.

The process of cerebral autoregulation maintains constant blood flow across a broad range of BP. For normotensive patients, the upper

threshold of this range is near a MAP of 150 mm Hg [18]. Patients with chronically uncontrolled hypertension adapt their cerebral vasculature and shift their threshold to the right [19,20]. Hypertension over time impairs vascular smooth muscle function, and vascular remodeling creates a tolerance for MAP values well over 150 mm Hg [11,21]. Due to these adaptations, many patients with markedly elevated BP in the ED are at low risk of acute BP-mediated injury. Conversely, there may be potential for harm with over-aggressive treatment, such as watershed ischemia [10,22].

Nearly all patients in this study were African Americans with uncontrolled hypertension of varying duration. We would have expected significant drops in cerebral flow velocity under two conditions: the pre-treatment BP was above the patient's upper threshold of cerebral autoregulation or a patient's drop in BP was so substantial that it exceeded the lower limit of cerebral autoregulation. On average, the study cohort did not meet either of these conditions. The cohort demonstrated a small mean change in cerebral flow velocity and no substantial difference in measurements of cerebral autoregulation between patients with intensive versus more modest BP reduction. There was a statistical difference in calculated CVRI change between patients with more intensive versus modest BP reduction. However, this difference only reflects greater BP reduction in the intensive group rather than differences in cerebral blood flow and autoregulation.

We suspect that the two patients who had adverse neurological events had falls in BP below their lower limit of cerebral autoregulation. The 5% prevalence of adverse neurological events raises concern for aggressive treatment in these patients. Retrospective analysis has not found increased adverse events associated with intravenous antihypertensive treatment, but such study methodology may have missed clinically significant events [9]. Prospective analysis of this practice is lacking in the literature and deserves further investigation. Despite guidelines recommending the contrary, intravenous antihypertensive treatment remains common both in the ED and in hospital setting for management of asymptomatic BP elevation [1,7,23].

Neuromonitoring for changes in cerebral blood flow and autoregulation remains a challenge in the ED setting. We used TCD because of its portability, ease of repeated measures, and robust volume of supporting literature in hypertension research [11,24,25]. Prior data has validated that MCA measurements are reproducible in the same patient with a difference $<3\%$ and a R-value of 0.95 between 2 measurements [26]. While we used a dedicated TCD machine, software and TCD probes are available for many existing common ED ultrasound machines. Transcranial Doppler has known shortcomings, including its limited assessment of the posterior circulation and its inability to measure focal changes in blood flow or tissue-level perfusion. The technique also assumes that MCA diameter does not change substantially with treatment, though prior research justifies this assumption for large capacitance vessels such as the MCA [27].

Other modalities for monitoring cerebral blood flow include magnetic resonance imaging (MRI), computed tomography perfusion (CTP) imaging, and cerebral oximetry. Using arterial spin-labeling, MRI can quantify global and localized tissue perfusion without the need for contrast agents [28]. Its primary limitation is availability in the emergent setting, particularly for repeated measures. Imaging with CTP can provide similar assessments of global and regional tissue perfusion. However, it requires iodinated contrast and exposes patients to ionizing radiation, a substantial problem with repeated measures. Non-invasive cerebral oximetry is widely used for repeated measurements in the perioperative setting [29]. This technology applies monitoring pads to the forehead that have near-infrared spectroscopy (NIRS) sensors to sample cerebral tissue oxygen saturation. It is portable and simple to use. While NIRS has promise for future research and clinical care in emergency care settings, its current shortcomings include contamination of measurements from underlying skin blood flow and its limitation to the frontal lobes [30].

Table 2
Hemodynamic characteristics.

Parameter	Pre-treatment	Delta ^a
	Mean (SD)	Mean (95% CI)
Vital signs		
Heart rate (bpm)	82 (16)	-13 (-17 to -9)
Mean arterial pressure (mm Hg)	149 (18)	-27 (-36 to -20)
Systolic blood pressure (mm Hg)	210 (26)	-38 (-49 to -27)
Diastolic blood pressure (mm Hg)	118 (17)	-33 (-39 to -26)
Cerebral hemodynamics		
Peak flow velocity (cm/s)	76 (17)	-7 (-12 to -3)
Diastolic flow velocity (cm/s)	36 (9)	-11 (-14 to -9)
Mean flow velocity (cm/s)	49 (11)	-5 (-7 to -2)
Cerebrovascular resistance index (mm Hg/cm/s)	3.2 (0.9)	-0.86 (-1.1 to -0.6)

^a Delta = difference of pre-treatment and post-treatment hemodynamic values.

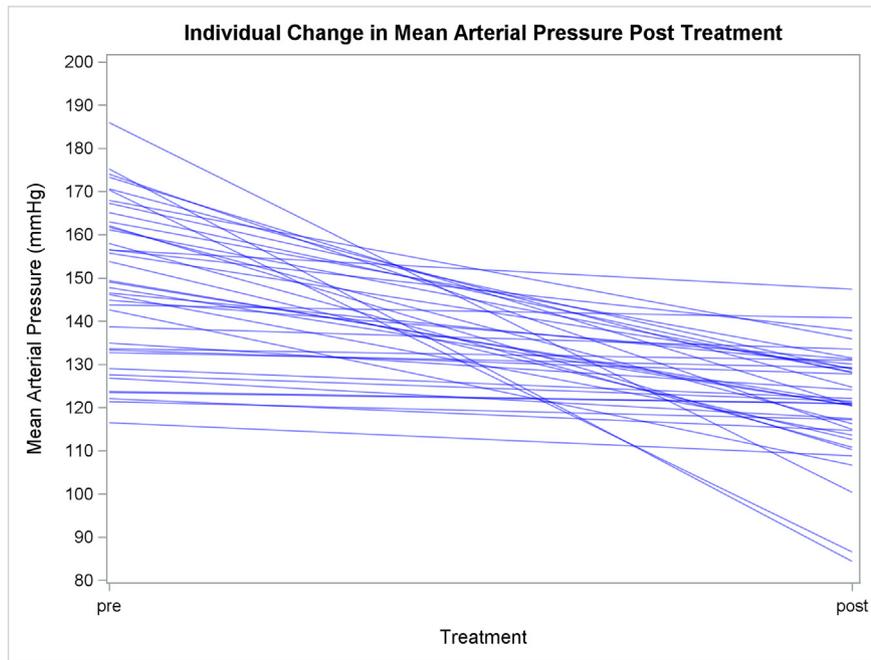


Fig. 1. Change in mean arterial pressure following treatment.

4.1. Limitations

Our study enrolled a convenience sample of patients with severely elevated BP and we did not specify specific reduction goals. The more modest BP reduction and greater variance in MFV measurements than anticipated limited our statistical power to detect significant drops in MCA flow velocity. A revised sample size estimate to detect a significant difference in MCA flow velocity change between patients with an intensive versus modest BP reduction with 80% power is 62 participants.

The requirement for patient consent significantly limited study participation prior to administration of antihypertensive agents. These factors may have introduced bias in the sample selection. This study was designed to measure the effect of BP change on cerebral flow rather than the effect of specific medications. We allowed for treatment with any antihypertensive class that the treating team felt was indicated. This design resulted in a significant heterogeneity of antihypertensive medications, and it is possible that antihypertensive class influenced study results. The design nonetheless allowed for an assessment of what happens in a real-world clinical setting. Finally, we did not

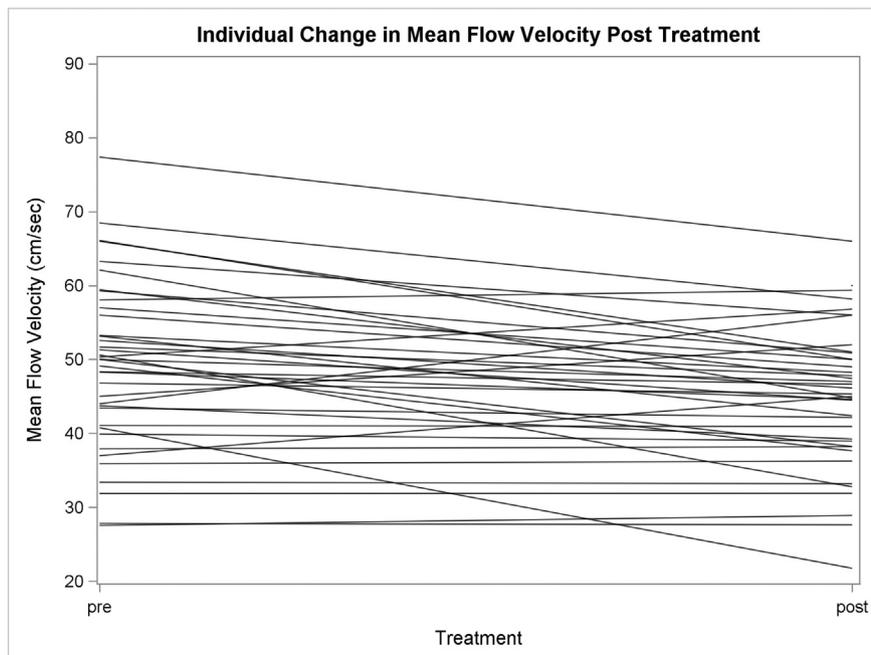


Fig. 2. Change in mean cerebral flow velocity following treatment.

Table 3
Comparison of hemodynamic change based on intensity of treatment.

Parameter	Non-intensive (n = 28)	Intensive (n = 11)	p-Value
	Mean (SD)	Mean (SD)	
Age, years	49 (11)	50 (15)	0.70
<i>Systemic hemodynamic delta</i>			
Heart rate (bpm)	−12 (11)	−15 (16)	0.58
Mean arterial pressure (mm Hg)	−16 (12)	−58 (19)	<0.01
Systolic blood pressure (mm Hg)	−23 (21)	−76 (28)	<0.01
Diastolic blood pressure (mm Hg)	−23 (11)	−56 (17)	<0.01
<i>Cerebral hemodynamic delta</i>			
Mean flow velocity (cm/s)	−4 (6)	−6 (10)	0.49
Cerebrovascular resistance index (mm Hg/cm/s)	−0.12 (0.48)	−0.86 (1.1)	0.05
Post-treatment Mx	0.18 (0.35)	0.21 (0.43)	0.36

systematically evaluate for the presence or absence of acute hypertensive target organ damage outside of clinical assessments through usual care. These considerations were beyond the scope of our pilot study but planned for future, related work.

5. Conclusion

This study did not find a substantial change in cerebral blood flow resultant from rapid reduction of BP. Nevertheless, it demonstrated the potential for adverse neurological events associated with rapid reduction of BP in patients that lacked clear indications for treatment.

Meetings

A portion of this work was presented as an abstract at the 16th International Symposium on Intracranial Pressure and Neuromonitoring, June 2016, Boston, MA.

Financial disclosure and conflicts of interest

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Author contributions

JBM and PL conceived the study, designed the protocol, and obtained research funding. JBM supervised the conduct of the study and data collection. SC, RT, BN, JBM, and EW undertook recruitment of patients and managed the data, including quality control. JBM and BR provided statistical advice on study design and analyzed the data. JBM drafted the manuscript, and all authors contributed substantially to its revision. JBM takes responsibility for the paper as a whole.

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