Ischemia in intracerebral hemorrhage: A comparative study of small-vessel and large-vessel diseases

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Abstract

Objective: This study aimed to compare effects of cerebral small-vessel disease (cSVD) burden and cerebral artery stenosis (CAS) on acute ischemia in intracerebral hemorrhage (ICH) and their interaction with mean arterial pressure (MAP) change. Methods: We recruited consecutive patients with acute primary ICH. Brain magnetic resonance imaging and angiography were performed to quantify diffusion-weighted imaging (DWI) lesions, CAS, and cSVD markers, which were calculated for the total cSVD score. Multivariable regression models were adopted to explore their associations by DWI lesions size (<15 vs. ≥15 mm) and median MAP change stratification. Results: Of 305 included patients (mean age 59.5 years, 67.9% males), 77 (25.2%) had DWI lesions (small, 79.2%; large, 20.8%) and 67 (22.0%) had moderate and severe CAS. In multivariable analysis, small DWI lesions were independently associated with higher total cSVD score (odds ratio [OR] 1.81, 95% confidence interval [CI] 1.36–2.41), and large DWI lesions were associated with more severe CAS (OR 2.51, 95% CI 1.17–5.38). This association was modified by MAP change (interaction p = 0.016), with stratified analysis showing an increased risk of large DWI lesions in severe CAS with greater MAP change (≥44 mmHg) (OR 3.48, 95% CI 1.13–10.74) but not with mild MAP change (<44 mmHg) (OR 1.21, 95% CI 0.20–7.34). Interpretation: Total cSVD burden is associated with small DWI lesions, whereas the degree of CAS is associated with large DWI lesions, specifically with greater MAP change, suggesting that large-artery atherosclerosis may be involved in ischemic brain injury, which is different from small-vessel pathogenesis in ICH.

Introduction

Primary intracerebral hemorrhage (ICH) is the second leading cause of death and disability in cases of stroke worldwide. The frustrating outcomes in patients with ICH highlight the need to better explore its potentially pathophysiological mechanisms. The development of magnetic resonance imaging (MRI) technology has provided the most potent approach to understanding the etiology of hemorrhage. Diffusion-weighted imaging (DWI) hyperintensities distant from the hematoma were considered to be acute ischemic lesions,1–5 which were identified in 11–41% of patients with acute ICH.2,4,6–8 They further aggravated brain injury. Most of these lesions were small, punctate, and asymptomatic, while patchy or medium to large lesions were often ignored. DWI lesions were not only associated with poor prognosis6,7,9,10 but also increased the risk of recurrent stroke.5,11–13 However, the underlying pathogenesis remains unclear. Most studies have associated DWI lesions with MRI markers of cerebral small-vessel disease (cSVD)6,14–17; some have associated them with blood pressure (BP) reduction,2,7,18 while others have argued against any correlation with BP reduction.9,19–21 However, to date, no study has combined...
magnetic resonance angiography (MRA) to evaluate DWI lesions in patients with ICH.

Hypertension and age are the most common risk factors for primary ICH. Long-term hypertension not only causes microangiopathies, such as cerebral microbleeds (CMBs), white matter hyperintensities (WMHs), and lacunes, but also induces large-artery atherosclerotic stenosis which may be subclinical before ICH. Large-vessel pathologies also exist in patients with ICH.\textsuperscript{22,23} However, few studies have comparatively analyzed the impact of small-vessel disease and large-artery atherosclerosis on patients with acute ICH. Whether the magnitude of BP change could influence this association needs to be further explored.

Therefore, we conducted a prospective study to explore the association of DWI lesions with total cSVD burden, degree of cerebral artery stenosis (CAS), and their interaction with mean arterial pressure (MAP) change, further elucidating the impact of microangiopathy and macroangiopathy on patients with acute ICH.

**Methods**

**Study population**

We performed a prospective observational study in patients with acute primary ICH from January 2017 to May 2021. Patients with acute ICH were consecutively enrolled from the stroke center of Zhengzhou People’s Hospital. The inclusion criteria were: (1) age $\geq$ 18 years; (2) ICH diagnosed by CT scan; (3) admitted to hospital within 24 hours of symptom onset; and (4) MRI scan was taken at 28 days after admission. The exclusion criteria were as follows: (1) isolated intraventricular hemorrhage; (2) secondary causes of ICH, such as hemorrhagic infarct, cerebral venous thrombosis, aneurysm, arteriovenous malformations, moyamoya disease, or brain tumor hemorrhage; (3) patients with incomplete clinical or MRI data. The study was approved by the Ethics Committee of Zhengzhou People’s Hospital and was in line with Helsinki guidelines. Informed consent was obtained from each patient or their legal surrogate.

**Data collection**

Patient data, including demographics, vascular risk factors (smoking, hypertension, diabetes mellitus, prior ischemic stroke, coronary artery disease, atrial fibrillation, and prior ICH), previous medication (antihypertensive drugs, antiplatelet drugs, anticoagulant drugs, statins), complications (deep venous thrombosis, pneumonia, stress ulcer), time to MRI scan, in-hospital intravenous antihypertensive treatment, laboratory tests, National Institute of

Health Stroke Scale (NIHSS) score, NIHSS change from admission to discharge, initial Glasgow Coma Scale (GCS) score, initial BP in the emergency department, and the highest and lowest BPs prior to MRI were collected. Delta MAP was calculated as the difference between the highest and lowest MAP prior to MRI.\textsuperscript{2,7} The likely etiologies of ICH were determined to be hypertensive angiopathy, probable cerebral amyloid angiopathy (CAA) according to classic Boston criteria,\textsuperscript{24} and anticoagulant-associated or undetermined cause.

**Neuroimaging measurements**

All patients underwent CT on admission and MRI on 1.5 or 3.0 T MR scanners within 28 days after admission. Imaging sequences included DWI with apparent diffusion coefficient (ADC) map, T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), susceptibility-weighted imaging (SWI), and MRA. Imaging parameters are shown in Data S1. DWI lesions were rated by a trained neuroradiologist (L.T.) with $\geq$5 years’ experience in neuroimaging review. CT, MRI, and MRA were assessed by two trained neuroradiologists (Y.S., P.Q.) blinded to the clinical information, and finally reached a consensus.

**Assessment of cSVD burden**

The imaging markers of cSVD included WMHs, enlarged perivascular spaces (EPVS), CMBs, and lacunes, which were evaluated according to STRIVE.\textsuperscript{25} The severity of WMHs was quantified using the Fazekas scale\textsuperscript{26} for periventricular white matter hyperintensities (PWMHs) and deep white matter hyperintensities (DWMHs) (range, 0–3); EPVS were quantified in the basal ganglia (BG) and centrum semiovale (CSO) regions (0 = no EPVS; 1 = 1–10 EPVS; 2 = 11–20 EPVS; 3 = 21–40 EPVS; 4 $\geq$ 40 EPVS)\textsuperscript{21}; CMBs were rated on SWI sequences as rounded or circular small hypointense foci with a diameter of 2–5 mm; lacunes were rated on FLAIR sequences as small, ovoid, fluid-filled cavities with a diameter of 3–15 mm. The cSVD burden was estimated by calculating the total cSVD score, where a point was awarded to each of the following (range, 0–4): (1) presence of lacunes; (2) presence of CMBs; (3) BG-EPVS $>$10; and (4) PWMHs with Fazekas score of 3 and/or DWMHs with Fazekas score of 2–3.

**Assessment of CAS**

The degree of CAS was evaluated on MRA according to WASID\textsuperscript{27} criteria including the intracranial segment of the internal carotid artery (ICA), A1 and A2 segment of anterior cerebral artery (ACA), M1 and M2 segment of
middle cerebral artery (MCA), P1 and P2 segment of posterior cerebral artery (PCA), vertebral artery, and basilar artery (BA). Patients were divided into three groups: mild stenosis group (<50%), moderate stenosis group (50–69%), and severe stenosis group (≥70%).

**Assessment of DWI lesions**

DWI lesions were defined as high-signal intensity lesions on DWI accompanied by low-signal intensity on ADC maps. DWI with high-signal intensity lesions in close (<10 mm) to the hematoma were excluded. The size, number, location, laterality relative to hematoma, and artery territories distribution of the DWI lesions were recorded. Small DWI lesions were defined as the maximum diameter of lesions <15 mm, and large DWI lesions were defined as the maximum diameter of lesions ≥15 mm.

**Statistical analysis**

Continuous variables with normal distributions were presented as means with standard deviations and were compared using the Student’s *t*-test. Variables with non-normal distributions were presented as medians with interquartile ranges (IQR) and were compared using the Mann–Whitney *U*-test. Categorical variables were described as numbers with percentages and were analyzed using χ² or Fisher’s exact test. Patients were stratified by the size of DWI lesions (<15 vs. ≥15 mm) and median MAP change (<44 vs. ≥44 mmHg), respectively. The associations between DWI lesions and total cSVD burden, degree of CAS, and the interaction with MAP fluctuation were investigated using multivariable logistic regression and stratified analysis after adjusting for clinically relevant variables and statically significant covariates (univariate variables with value of *p* < 0.10). The result was presented as odds ratio (OR) and 95% confidence interval (CI). We examined the multicollinearity and interaction effects of the covariates. Two-tailed *p* < 0.05 were considered statistically significant. All analyses were performed using SPSS (version 25.0; IBM Statistics, Armonk, NY, USA).

**Results**

**Clinical and imaging characteristics**

A total of 305 patients with acute ICH were finally included in this study. The flowchart of patients selection is presented in Figure 1. The mean age of these patients was 59.5 ± 12.6 years and 67.9% were male. Of the 305 patients, 111 (36.4%) patients were given intravenous antihypertensive treatment in-hospital; of them, urapidil was administered in 80 cases (72.1%), nicardipine in 25 cases (22.5%), nimodipine in 10 cases (9.0%), and nitroprusside in 3 cases (2.7%). Table 1 shows the clinical and imaging characteristics of all patients and subgroups without DWI lesions, with small DWI lesions, and with large DWI lesions. Compared to patients without DWI lesions, patients with small DWI lesions were more likely to have greater MAP change (48 vs. 43 mmHg, *p* = 0.019), higher initial systolic blood pressure (SBP) (174 vs. 166 mmHg, *p* = 0.017), higher hemoglobin Alc (5.8% vs. 5.5%, *p* = 0.025), higher rates of deep venous thrombosis (11.5% vs. 3.5%, *p* = 0.030), and higher total cSVD score (3 vs. 1, *p* < 0.001). Each marker of cSVD was significantly different in patients with small DWI lesions versus without DWI lesions, but the distribution of moderate to severe CAS did not differ. Patients with large DWI lesions were more likely to have a history of ischemic stroke (50.0% vs. 23.7%, *p* = 0.041), greater MAP change (52 vs. 43 mmHg, *p* = 0.008), higher initial SBP (185 vs. 166 mmHg, *p* = 0.018), higher rates of deep venous thrombosis (18.8% vs. 3.5%, *p* = 0.028), and more moderate to severe stenosis of ICA (56.3% vs. 3.1%, *p* < 0.001), MCA (50.0% vs. 10.1%, *p* < 0.001), and PCA (25.0% vs. 7.5%, *p* = 0.041) than patients without DWI lesions. No significant differences were observed in each marker of cSVD and total cSVD score in patients with large DWI lesions versus without DWI lesions.

**Characteristics of DWI lesions**

Among 305 patients, 25.2% (77/305) patients presented with DWI lesions (Imaging examples Fig. 2). Of these, 79.2% (61/77) had small DWI lesions, 20.8% (16/77) had large DWI lesions. The median diameter of small DWI lesions was 3 (IQR 2–7) mm, 88.5% were asymptomatic infarction, and the median diameter of large DWI lesions was 21 (IQR 16–38) mm, all of which were symptomatic infarction. Overall, 12.5% (38/305) had multiple lesions which were mostly small DWI lesions (84.2%) (punctate, round, or ovoid) with an increasing trend in proportion with the increasing number of DWI lesions (Fig. 3A). Small DWI lesions were mainly located in the cortical and subcortical regions of lobes (65%) and scattered in multiple vascular territories (66.7%). Large DWI lesions were mostly single, mainly located in deep structures (56.3%), contralateral to the hematoma (68.8%), and in moderately to severely stenosed arterial territories (77.8%) (Fig. 3B–D).

**Association between cSVD burden and different sizes of DWI lesions**

The distribution of total cSVD burden was significantly different among the groups (*p* = 0.001, Fig. 4A).
Patients with small DWI lesions had a higher total cSVD burden than those without DWI lesions \( (p < 0.001) \). The cSVD burden was positively correlated with the number of small DWI lesions \( (r = 0.221, \ p < 0.001) \). In multivariable analyses, a high cSVD burden was independently associated with small DWI lesions \( (OR 1.81, 95\% CI 1.36–2.41, \ p < 0.001) \) (Fig. 5) but not with large DWI lesions \( (OR 0.83, 95\% CI 0.47–1.43, \ p = 0.490) \) (Fig. 6).

**Association between the degree of CAS and different sizes of DWI lesions**

Moderate to severe CAS was observed in 22.0% (67/305) patients. The degree of CAS was significantly different among the groups \( (p = 0.029, \) Fig. 4B). Compared to patients without DWI lesions, patients with large DWI lesions had more severe CAS \( (p = 0.006) \), especially in the ICA and MCA. Multivariable analyses showed that CAS...
### Table 1. Clinical and imaging characteristics of ICH patients.

| Variables                                | All           | Without DWI lesions | With DWI lesions | p-value |
|------------------------------------------|---------------|---------------------|------------------|---------|
|                                          | All (100)     | Small (100)         | Large (50)       |         |
| N (%)                                    | 305 (100)     | 228 (74.8)          | 61 (20.0)        | 16 (5.2) |
| Demographic                              |               |                     |                  |         |
| Age, (years), mean (SD)                  | 59.5 (12.6)   | 58.9 (12.8)         | 61.3 (12.1)      | 61.8 (12.1) |
| Male, n (%)                              | 207 (67.9)    | 156 (68.4)          | 39 (63.9)        | 12 (75.0) |
| Vascular risk factors, n (%)             |               |                     |                  |         |
| Hypertension                             | 243 (79.7)    | 178 (78.1)          | 51 (83.6)        | 14 (87.5) |
| Diabetes mellitus                        | 84 (27.5)     | 56 (24.6)           | 23 (37.7)        | 5 (31.3) |
| Coronary artery disease                  | 54 (17.7)     | 37 (16.2)           | 13 (21.3)        | 4 (25.0) |
| Atrial fibrillation                      | 9 (3.0)       | 8 (3.5)             | 1 (1.6)          | 0 (0)   |
| Prior ischemic stroke                    | 83 (27.2)     | 54 (23.7)           | 21 (34.4)        | 8 (50.0) |
| Prior ICH                                | 52 (17.0)     | 38 (16.7)           | 16 (16.4)        | 4 (25.0) |
| Smoking, current or quit <5 years        | 108 (35.4)    | 78 (34.2)           | 22 (36.1)        | 8 (50.0) |
| Body mass index, (kg/m²), median (IQR)   | 25.2 (22.9–28.1) | 24.9 (22.7–28.0) | 25.4 (23.2–29.3) | 27.0 (22.9–29.4) |
| Previous medication, n (%)               |               |                     |                  |         |
| Antihypertensive drugs                   | 164 (53.8)    | 117 (51.3)          | 38 (62.3)        | 9 (56.3) |
| Antiplatelet drugs                       | 56 (18.4)     | 36 (15.8)           | 15 (24.6)        | 5 (31.3) |
| Oral anticoagulants                      | 5 (1.6)       | 2 (0.9)             | 2 (3.3)          | 1 (6.3) |
| Statins                                  | 47 (15.4)     | 30 (13.2)           | 13 (21.3)        | 4 (25.0) |
| Complication, n (%)                      |               |                     |                  |         |
| Deep venous thrombosis                   | 18 (5.9)      | 8 (3.5)             | 7 (11.5)         | 3 (18.8) |
| Pneumonia                                | 89 (29.2)     | 58 (25.4)           | 23 (37.7)        | 8 (50.0) |
| Stress ulcer                             | 20 (6.6)      | 16 (7.0)            | 2 (3.3)          | 2 (12.5) |
| Clinical features                        |               |                     |                  |         |
| NIHSS at admission, median (IQR)         | 5 (3–12)      | 5 (3–11)            | 4 (2–13)         | 8 (3–13) |
| NIHSS change from admission to discharge, median (IQR) | 2 (1–5) | 3 (1–6) | 2 (0–5) | 1 (–1–2) |
| Initial GCS, median (IQR)                | 15 (14–15)    | 15 (14–15)          | 15 (14–15)       | 15 (14–15) |
| Time to MRI, (day), median (IQR)         | 11 (6–16)     | 11 (6–16)           | 12 (6–16)        | 8 (6–12) |
| Initial SBP, (mmHg), median (IQR)        | 168 (153–186) | 166 (152–185)       | 174 (164–187)    | 185 (161–197) |
| Initial DBP, (mmHg), median (IQR)        | 100 (88–110)  | 97 (85–112)         | 101 (95–110)     | 100 (96–113) |
| Delta MAP, (mmHg), median (IQR)          | 44 (35–54)    | 43 (35–52)          | 48 (38–62)       | 52 (41–64) |
| Intravenous antihypertensive treatment   | 111 (36.4)    | 83 (36.4)           | 19 (31.1)        | 9 (56.3) |
| in-hospital, n (%)                       |               |                     |                  |         |
| Presumed etiology of ICH, n (%)           |               |                     |                  |         |
| Hypertensive angiopathy                   | 210 (68.9)    | 153 (67.1)          | 44 (72.1)        | 13 (81.3) |
| Cerebral amyloid angiopathy               | 36 (11.8)     | 26 (11.4)           | 10 (16.4)        | 0 (0)   |
| Anticoagulation or undetermined cause     | 59 (19.3)     | 49 (21.5)           | 7 (11.5)         | 3 (18.8) |
| Laboratory tests                          |               |                     |                  |         |
| WBC, (×10⁹/L), median (IQR)              | 7.4 (5.8–9.4) | 7.4 (5.8–9.1)       | 7.5 (5.8–10.2)   | 8.2 (6.0–10.0) |
| Neutrophil, ×10⁹/L, median (IQR)          | 5.3 (3.9–7.1) | 5.3 (3.8–6.7)       | 5.5 (3.9–7.3)    | 6.0 (3.2–7.9) |
| Triglyceride, (mmol/L), median (IQR)      | 1.3 (0.8–1.9) | 1.3 (0.8–1.7)       | 1.2 (0.8–2.3)    | 1.2 (0.8–1.7) |
| Total cholesterol (mmol/L), median (IQR)  | 4.4 (3.6–5.0) | 4.3 (3.6–4.9)       | 4.5 (3.5–5.3)    | 4.7 (3.7–5.6) |
| LDL-C, (mmol/L), median (SD)              | 2.6 (1.0)     | 2.5 (1.0)           | 2.6 (0.9)        | 2.9 (1.0) |
| Homocysteine, (μmol/L), median (IQR)      | 14.6 (11.8–18.6) | 14.6 (11.5–19.2) | 14.6 (12.7–17.7) | 13.5 (10.6–14.9) |
| HbA1C (%), median (IQR)                   | 5.6 (5.2–6.0) | 5.5 (5.1–5.9)       | 5.8 (5.2–6.8)    | 5.6 (5.4–6.0) |
| Fasting blood glucose (mmol/L), median (IQR) | 6.3 (5.2–7.5) | 6.0 (5.1–7.5)       | 6.5 (5.3–7.8)    | 6.8 (5.9–7.6) |
| Fibrinogen, (g/L), median (IQR)           | 2.5 (2.1–3.1) | 2.5 (2.1–3.0)       | 2.6 (2.1–3.2)    | 2.5 (2.3–3.7) |
| CT findings                               |               |                     |                  |         |
| Location of hematoma, n (%)               |               |                     |                  |         |
| Deep                                     | 219 (71.8)    | 167 (73.2)          | 39 (63.9)        | 13 (81.3) |
| Lobar                                    | 70 (23.0)     | 51 (22.4)           | 17 (27.9)        | 2 (12.5) |
| Infratentorial                           | 21 (6.9)      | 13 (5.7)            | 7 (11.5)         | 1 (6.2) |
| Intraventricular extension                | 73 (23.9)     | 52 (22.8)           | 17 (27.9)        | 4 (25.0) |

(Continued)
was independently associated with large DWI lesions (OR 2.51, 95% CI 1.17–5.38, \( p = 0.018 \) (Fig. 6) but not with small DWI lesions (OR 1.16, 95% CI 0.69–1.96, \( p = 0.580 \)) (Fig. 5).

When stratified analysis (Table 2) by median MAP change (<44 vs. \( \geq 44 \) mmHg) was performed, more severe CAS was associated with increased risk of large DWI lesions with greater MAP change (OR 3.48, 95% CI 1.13–10.74, \( p = 0.030 \)) but not with mild MAP change (OR 1.26, 95% CI 0.32–4.93, \( p = 0.737 \)). This association between CAS and large DWI lesions was modified by MAP change (interaction term: OR 2.75, 95% CI 1.21–6.26, \( p = 0.016 \)). While the association between total cSVD burden and small DWI lesions was not modified by MAP change (interaction term: OR: 0.91, 95% CI 0.59–1.40, \( p = 0.665 \)).

### Discussion

In this study, we demonstrated that a high burden of cSVD was independently associated with the presence of small DWI lesions in acute primary ICH, regardless of MAP change. Severe CAS was independently associated with the presence of large DWI lesions. This association was modified by MAP change, with stratified analysis showing an increased risk of large DWI lesions in severe CAS with greater MAP change but not with mild MAP change. The greater MAP change drove most of the association. Previous studies have reported that DWI lesions were linked to small-vessel arteriopathy\(^5,6,15,17\) or intensive BP reduction.\(^2,7,18\) However, they may be insufficient to explain the DWI lesions of different sizes, frequencies, and vascular territories in patients with ICH. MRA data
on whether these lesions were linked to a specific stenosed artery territory is still lacking. We found that large DWI lesions were mostly single, mainly located in deep structures, contralateral to the hematoma, and in moderately to severely stenosed artery territory. Whereas small lesions were more likely to be multiple, mainly located in the cortical and subcortical regions, and scattered in multiple vascular territories. Moreover, the number of small lesions was positively correlated with the total cSVD burden. These findings confirmed that large-artery lesions were linked to a specific stenosed artery territory.
Atherosclerosis was also involved in ischemic brain injury, differing from the small-vessel pathogenic mechanisms in ICH.

The precise pathophysiological mechanisms of DWI lesions in acute ICH are not yet well understood. Most studies have reported that ischemic lesions were related to CMB,6,7,15 WMHs,6,7,15–17 and CSO-EPVS,15,20 but few reported a relationship to lacunes. Our analysis showed that all MRI markers of cSVD were associated with small DWI lesions adjustment for other established confounding factors. This may be due, in part, to the lack of stratified analysis based on lesion size, because they have different pathogenesis. A single imaging marker of cSVD to estimate the overall impact of small-vessel pathology is

Figure 3. Number, size, location, and distribution of DWI lesions. (A) Number and size of DWI lesions; (B) location of DWI lesions; (C) laterality relative to hematoma; (D) territory distribution in moderate to severe artery stenosis. DWI, diffusion-weighted imaging.

Figure 4. (A) Distribution of total cSVD burden. (B) Distribution of cerebral artery stenosis. cSVD, cerebral small-vessel disease.
limited. Therefore, an MRI-based cSVD score was proposed to capture the overall burden of small vessel disease. We found the total cSVD score was better at revealing the association between the cSVD burden and small DWI lesions. Small DWI lesions may be a manifestation of active vasculopathy and coexist with ICH or present secondarily after ICH. A longitudinal study observed that 35% of patients had DWI lesions at baseline, and 22% had new DWI lesions at 1 month that had not been present at baseline, while another longitudinal study indicated that 50% had new DWI lesions at 1 week. Patients with microangiopathy had reduced cerebral autoregulation. Whether there is an interaction between cSVD and MAP change on ICH has not been previously studied. We found no significant interaction between them.

ICH and ischemic stroke share common atherosclerotic risk factors such as hypertension and advancing age. Little attention has been paid to the effect of large-artery atherosclerosis on ICH. In our cohort, 22.0% of patients had moderate to severe CAS. Among them, ICA and MCA stenosis were especially associated with large DWI lesions. Some of the large lesions were borderzone infarctions, indicating the potential mechanism of hypoperfusion. Interestingly, when the hematoma was contralateral to the hemisphere with severe CAS, infarcts were mostly distributed in the severely stenotic artery territory; however, when the hemorrhage was ipsilateral to severe CAS, the infarcts were mostly located in the contralateral territory. The most likely explanation is the possible involvement of an artery steal blood mechanism. In addition, local thrombosis and artery-to-artery embolism may occur more frequently in patients with multiple atherosclerotic stenoses during the stress state of ICH, hemodynamic compromise, intracranial hypertension decreasing cerebral perfusion pressure, dehydration drugs resulting in reduced blood volume, and proinflammatory cascades. Reports regarding the relationship between BP lowering and DWI lesions remain conflicting. In our study, MAP lowering alone was not associated with ischemia, which differed from the views of those supporting BP reduction. Only in the setting of severe vasculopathy, aggressive change of BP was more likely to induce brain ischemic injury. There was a significant interaction of MAP change and severe underlying large-artery atherosclerosis on ICH. The hypothesis that patients with large artery atherosclerotic changes are at greater risk of developing ischemic lesions after BP lowering should be

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**Figure 5.** Multivariate analysis for the association of small DWI lesions with cSVD and CAS. Adjusted for age, sex, body mass index, hypertension, diabetes mellitus, ischemic stroke, smoking, initial systolic blood pressure, initial hematoma volume, subarachnoid extension, pneumonia, initial National Institute of Health Stroke Scale, hemoglobin A1c, delta MAP, and CAS. DWI, diffusion-weighted imaging; cSVD, cerebral small-vessel disease; CAS, cerebral artery stenosis; MAP, mean arterial pressure.

| Variable                  | Adjusted OR (95% CI) | P value |
|---------------------------|----------------------|---------|
| Total cSVD score          | 1.81 (1.36-2.41)     | <0.001* |
| BG-EPVS                   | 1.66 (1.12-2.47)     | 0.012*  |
| CSO-EPVS                  | 1.91 (1.31-2.79)     | 0.001*  |
| PWMHs                     | 2.19 (1.40-3.43)     | 0.001*  |
| DWMHs                     | 1.99 (1.29-3.09)     | 0.002*  |
| Moderate to severe WMHs   | 3.15 (1.47-6.76)     | 0.003*  |
| Presence of lacunes       | 2.24 (1.13-4.41)     | 0.020*  |
| Number of lacunes         | 1.22 (1.02-1.46)     | 0.033*  |
| Presence of CMBS          | 2.98 (1.32-6.73)     | 0.008*  |
| Deep CMBS                 | 1.06 (1.01-1.11)     | 0.031*  |
| Lobar CMBS                | 1.02 (0.94-1.11)     | 0.629   |
| Delta MAP                 | 1.01 (0.99-1.04)     | 0.381   |
| Degree of artery stenosis | 1.16 (0.69-1.96)     | 0.580   |

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tested in future randomized trials. Intensive BP lowering cannot improve overall outcomes without considering individual differences.\textsuperscript{31–36}

Certain limitations of this study warrant consideration. First, selection bias was unavoidable owing to the lack of MRI in patients with severe hemorrhage. Second, MRI
could not be performed at the same time points because of the different severities of the ICH patients. Third, extracranial vessels were not assessed because patients with acute ICH cannot cooperate with long-time MRI. Finally, the cross-sectional study could not inform the direction of the association of DWI lesions with cSVD burden and CAS. Further longitudinal MRI studies should clarify whether these lesions are coexisting or secondary, and change in trends over time. However, this study has strengths. This study combining MRI and MRA for the first time compared the contribution of small-vessel disease burden and large-artery atherosclerotic burden to DWI lesions, and the interaction with MAP change in patients with acute ICH. In addition, the size, number, location relative to hematoma, and artery watershed distribution of the DWI lesions were also fully analyzed.

Conclusions

This study confirms that a high cSVD burden is independently associated with small DWI lesions, while severe CAS is independently associated with large DWI lesions, specifically with greater MAP change. Long-term hypertensive vasculopathy may be a prevailing mechanism. These findings provide convincing evidence that ischemic brain injury in acute ICH is not only associated with greater microangiopathy burden but also with large-artery atherosclerosis burden. It has important implications for developing optimal interventions for individualized BP control targets for subjects with different degrees of brain atherosclerosis to prevent further ischemic injury.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Author Contributions

Ailing Zhang, Mengyang Ren, and Wenjing Deng participated in the conception and design of the study and manuscript drafting. Meijing Xi, Long Tian, Zhuoya Han, Weiping Zang, and Hao Hu participated in the acquisition and analysis of data. Bin Zhang, Ling Cui, Peihong Qi, and Yingjie Shang contributed to data collection, analysis, and manuscript revision. All authors substantially contributed to this manuscript and approved the final version.

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Supporting Information
Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1. Imaging parameters of MRI and MRA.