



## Analysis of Hemorrhage Volumes After Angiogram-Negative Subarachnoid Hemorrhage

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■ **BACKGROUND:** Antiplatelet medication use is associated with worsened outcome after angiogram-negative subarachnoid hemorrhage (SAH). It has been hypothesized that these worsened outcomes may be the result of an association between antiplatelet medication use and increased hemorrhage volumes after angiogram-negative SAH. To test this hypothesis, we performed volumetric analysis of computed tomography (CT)-defined hemorrhage after angiogram-negative SAH.

■ **METHODS:** This was a retrospective analysis of patients presenting with nontraumatic, angiogram-negative SAH in the Columbia University Subarachnoid Hemorrhage Outcomes database between 2000 and 2013. SAH volumes on admission head CT scans were measured using the MIPAV software package, version 7.20 in a semiautomated fashion.

■ **RESULTS:** A total of 108 presenting CT scans from patients with angiogram-negative SAH were analyzed. The mean hemorrhage volume was 14.3 mL in the patients with a history of antiplatelet medication use, compared with 6.8 mL in those with no history of antiplatelet use. This difference was found to be significant ( $P = 0.0029$ ).

■ **CONCLUSIONS:** Antiplatelet medication use is associated with increased SAH volumes in patients with angiogram-negative SAH. Increased hemorrhage volumes may contribute to poor outcomes in this patient population. Prospective studies are warranted to confirm this association.

Antiplatelet drugs are among the most commonly used medications worldwide.<sup>1,2</sup> The efficacy of these drugs, including aspirin and clopidogrel, in the prevention and treatment of thrombotic vascular disease has fueled their widespread use, especially in developed countries.<sup>3,4</sup> Antiplatelet therapy is now a mainstay in the treatment of patients with such common conditions as unstable angina, coronary artery disease, peripheral artery disease, atrial fibrillation, and myocardial infarction.<sup>5-9</sup> In addition, the progressive increase in the use of percutaneous coronary interventions, including stenting, adds more than 1 million patients per year to the population receiving single or dual antiplatelet therapy.<sup>10,11</sup> Most patients with previous thromboembolic or ischemic stroke are prescribed antiplatelet therapy.<sup>12,13</sup> Although the benefits of antiplatelet therapies are unquestionable, serious hemorrhagic complications can result from their use.<sup>14-17</sup>

Angiogram-negative subarachnoid hemorrhage (SAH), or nonaneurysmal SAH, is a unique variant of SAH for which no structural aberration can be found as a cause for the spontaneous hemorrhage.<sup>18,19</sup> It accounts for approximately 10%–20% cases of SAH, appears to be rising in frequency, and may be associated with poor clinical outcomes, similar to those observed with aneurysmal SAH.<sup>18,20-32</sup> Recent literature suggests that hemorrhage patterns may be correlated with clinical outcomes, although hemorrhage volume has heretofore not been rigorously evaluated as a prognostic indicator in angiogram-negative SAH.<sup>20,21,33-35</sup>

Angiogram-negative SAH is further subdivided into 2 distinct entities by bleeding pattern on the diagnostic computed tomography (CT) scan: perimesencephalic and nonperimesencephalic/diffuse. Perimesencephalic SAH is thought to be secondary to venous bleeding and has a good prognosis.<sup>18</sup> Nonperimesencephalic or diffuse angiogram-negative SAH may approach aneurysmal SAH in clinical severity and prognosis.<sup>21,36</sup>

### Key words

- Aneurysm
- Aspirin
- Clopidogrel
- Intracranial hemorrhage
- Stroke

### Abbreviations and Acronyms

**CT:** Computed tomography

**SAH:** Subarachnoid hemorrhage

**SHOP:** Subarachnoid hemorrhage outcomes project

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Recent studies using the Columbia University Medical Center's Subarachnoid Hemorrhage Outcomes Project (SHOP) database have demonstrated that antiplatelet therapy may be associated with poor outcomes in patients with angiogram-negative SAH.<sup>37</sup> This and other studies have suggested that the increased use of antiplatelet medications may be linked to the rise in angiogram-negative SAH, although additional research is needed to confirm this association.<sup>38-40</sup> Whereas the prognostic value of hemorrhage volume and location in patients with hemorrhagic stroke has been previously suggested, we are unaware of any previous studies associating antiplatelet use with hemorrhage volumes in angiogram-negative SAH.<sup>35,41-46</sup> Thus, in the present study we tested the hypothesis that a history of antiplatelet medication use is associated with increased hemorrhage volumes in patients with angiogram-negative SAH.

## METHODS

### Study Population

All patients with nontraumatic SAH detected on head CT scan at the time of admission were prospectively enrolled in the Columbia University Medical Center's SHOP database between 2000 and 2013. Patients were designated as "angiogram-negative" when no lesion was found on catheter angiogram. Patient demographic and historical data were also collected in the SHOP database at the time of admission.

### Management of SAH

Our institution's approach to management of SAH has been described previously.<sup>47</sup> Patients presenting with a history suspicious of SAH receive a noncontrast head CT scan. On diagnosis of SAH, all antithrombotic medications are held, and reversed when applicable. Antiplatelet medications are

discontinued, and platelet transfusion is initiated. Patients with angiogram-negative SAH receive at least 2 cerebral angiograms during their admission.

### Variables and Volumetric Quantification

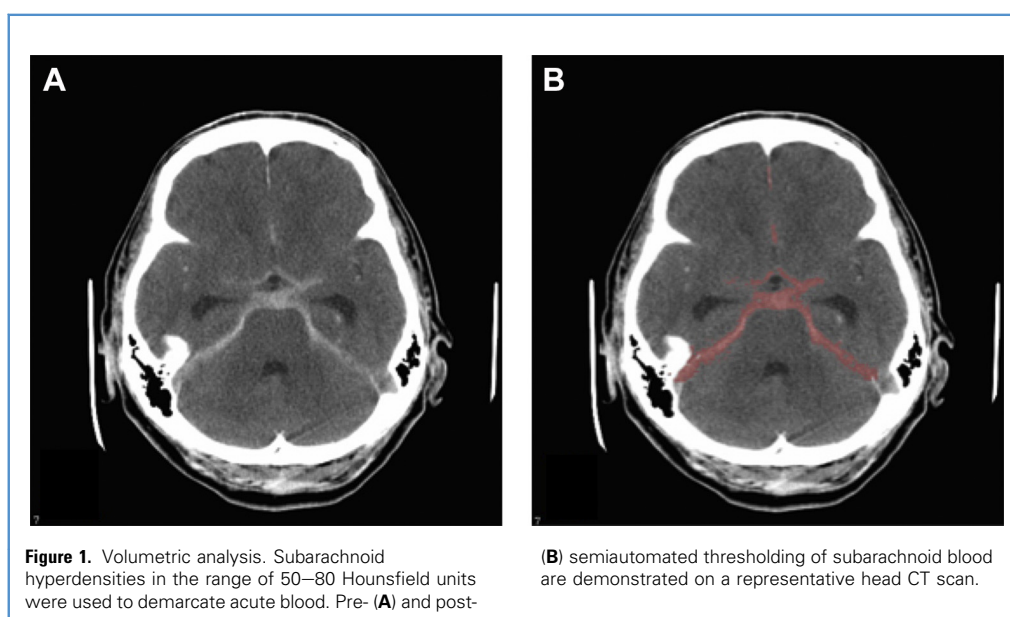
Baseline data, including age, sex, admission Hunt–Hess grade, and history of antiplatelet medication use, were collected. No specific antiplatelet medications were retrospectively recorded in the database. Available head CT scans from patients who underwent conventional catheter angiography after presenting with nontraumatic SAH were reviewed. Hemorrhage volumes were measured using the MIPAV software package, version 7.20 (National Institutes of Health, Bethesda, MD, USA) in a semi-automated fashion as validated previously (Figure 1).<sup>44,45,48</sup>

### Statistical Analysis

All statistical analyses were performed using Stata 14 (StataCorp, College Station, TX, USA). Student's *t* test was used for continuous variables and the  $\chi^2$  test was used for categorical variables in univariate analyses. Multivariate analysis was performed using a multiple logistic regression model adjusting for age, sex, and admission Hunt–Hess grade. A *P* value or Pearson's coefficient  $\leq 0.05$  was considered significant.

## RESULTS

A total of 1582 patients with nontraumatic SAH were enrolled in the SHOP database during the study period. Of these 1582 patients, 1351 underwent catheter cerebral angiography during their admission. No structural cause of hemorrhage was found for the 173 patients who were diagnosed with angiogram-negative SAH. Among these 173 patients, 108 had a head CT scan obtainable from our medical records database (Table 1). Forty-three of these 108 patients (40%) received an antiplatelet



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