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# Systolic Blood Pressure Variability is a Novel Risk Factor for Rebleeding in Acute Subarachnoid Hemorrhage

## A Case–Control Study

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**Abstract:** Rebleeding of an aneurysm is a major cause of morbidity and mortality after subarachnoid hemorrhage (SAH). Whereas numerous studies have demonstrated predictors of rebleeding and effect of systolic blood pressure variability (SBPV) on stroke, few data on the association between SBPV and rebleeding.

Here, we sought to identify the effect of SBPV on rebleeding in acute aneurysmal SAH.

Case–control study.

From January 2010 to June 2015, 612 patients with aneurysmal SAH were enrolled in our tertiary care medical center.

Main outcome measures: Consecutive patients with acute (<3 days from ictus) aneurysmal rebleeding or repair or death were retrospectively included. Antihypertensive therapy based on a predefined standardized protocol was prescribed to lower and maintain SBP between 120 and 160 mm Hg. SBP was measured hourly until a censoring event occurred. SBPV was determined as standard deviation (SD) and successive variation (SV). Binary logistic regression was used to assess the association between SBPV and rebleeding.

Rebleeding occurred in 61 (10.0%) of the 612 patients. We identified 47 acute rebleeding as cases and 382 early repair or early death as controls. On binary logistic regression analysis, rebleeding was associated with the SD of SBP (odds ratio [OR], 1.254; 95% confidence interval [CI], 1.131–1.391;  $P < 0.001$ ) and the SV of SBP (OR, 1.131; 95% CI, 1.039–1.231;  $P = 0.004$ ). No significant difference was seen between rebleeding and mean systolic blood pressure (MSBP).

SBPV is associated with increased rates of acute aneurysmal rebleeding. Further prospective research is warranted to confirm that SBP stability prevents acute aneurysm rebleeding.

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**Abbreviations:** CI = confidence interval, CT = computed tomography, mRS = modified Rankin Scale, MSBP = mean systolic blood pressure, OR = odds ratio, SAH = subarachnoid hemorrhage, SBPV = systolic blood pressure variability, SD = standard deviation, SV = successive variation.

## INTRODUCTION

Aneurysm rebleeding is a leading cause of mortality and morbidity.<sup>1–3</sup> Despite studies demonstrating the safety of early obliteration,<sup>4–6</sup> the rate of rebleeding is still high.<sup>3,6,7</sup> Most studies reveal that rebleeding often occurs within 3 days of the presenting hemorrhage.<sup>5,7–9</sup> Therefore, it will be beneficial to identify a subgroup of patients with high risk of rebleeding in the acute phase of subarachnoid hemorrhage (SAH).

Since then, many factors associating with an increased risk for rebleeding have been investigated, including high blood pressure,<sup>5,10–12</sup> poor Hunt–Hess grade,<sup>13</sup> number of aneurysms,<sup>14</sup> large aneurysm size,<sup>5,15</sup> early angiography,<sup>9,16</sup> and so on. However, there are discrepancies regarding the significance of many of these predictors.<sup>17</sup>

Systolic blood pressure variability (SBPV) is a newly defined concept which appears to be a good predictor of stroke.<sup>18,19</sup> Accordingly, high SBPV may increase the risk of rebleeding in acute SAH. However, since then, there has been no study which reports an association between SBPV and rebleeding. Therefore, we sought to investigate the association between SBPV and rebleeding in acute SAH.

## Materials and Methods

We retrospectively enrolled 612 consecutive patients with aneurysmal SAH admitted to the First Affiliated Hospital of Fujian Medical University, Fuzhou, China, from January 2010 to June 2015. To be included, case subjects had to be patients who rebled within 3 days of ictus, control subjects had to be patients whose aneurysm was repaired within 3 days of ictus or patients who died within 3 days of ictus. The exclusion criteria were suspicion of rebleeding but without confirmation by the subsequent computed tomography (CT) scans, rebleeding after aneurysm repair, combined other vascular malformation, history of SAH, coagulation disorders including patients on antiplatelets or anticoagulants. Demographic, historical, and medical data were collected by 2 investigators independently. The study was approved by the hospital's institutional review board.

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Brachial cuff blood pressure values were recorded every 1 hour until a censoring event (rebleeding, aneurysm repair, or death) occurred. Only measurements prior to rebleeding in cases and only prior to aneurysm repair, death in controls were utilized. All death in controls was caused by severe initial bleed and secondary failure of respiratory and circulatory function. They were excluded from rebleeding by the following CT scan and/or autopsy. Mean systolic blood pressure (MSBP) was calculated as the average of all SBP values. SBPV was quantified by calculating standard deviation (SD) and successive variation (SV) based on the successive SBP values measured hourly with the following formulas:

$$\text{SD: } \sqrt{1/(n-1) \sum_{(i=1)}^{(n-1)} (BP_i - BP_{mean})^2} \text{ and}$$

$$\text{SV: } \sqrt{1/(n-1) \sum_{(i=1)}^{(n-1)} (BP_{i+1} - BP_i)^2},$$

respectively.<sup>19</sup> SAH was diagnosed by the admission CT scan or by the presence of blood and xanthochromia of the cerebrospinal fluid if the CT was not diagnostic. Features of aneurysm were identified by CT angiography or digital subtraction angiography. For assessment of rebleeding, all patients were followed up until the episode of rebleeding, surgery, discharge, or death. Rebleeding was defined as a sudden deterioration in neurological status with evidence of new bleed apparent on CT. Each episode of rebleeding was reconfirmed independently by a 2nd investigator by review of the CT and medical record. Cases with a high clinical suspicion of rebleeding but without confirmation by the subsequent CT scans were not included.

The medical management of patients with aneurysmal SAH at our institution was according to the guidelines.<sup>12,20</sup> The CT scans were obtained on admission and at every major clinical event. Aneurysm repair was performed whenever possible. Antifibrinolytic drug was administered at the 1st 3 days of initial hemorrhage. Intravenous nimodipine was routinely given at a speed of 1.2 mg/h. Patients with high SBP received antihypertensive therapy based on a predefined standardized protocol to lower and maintain SBP between 120 and 160 mm Hg using intravenous nimodipine or sodium nitroprusside or urapidil hydrochloride. An external ventricular drain was placed in patients with symptomatic hydrocephalus or intraventricular hemorrhage with depressed level of consciousness. Outcome was assessed according to the modified Rankin Scale (mRS) at discharge.

Categorical variables were tested with the Fisher exact test or  $\chi^2$  test; continuous variables were analyzed with the Mann-Whitney *U*-test or *t*-test. Variables with *P* value less than 0.10 on univariate analysis were entered into a binary logistic regression analysis to identify the independent baseline predictors. The statistical analysis was conducted in 2 parts, which included the analysis of the association between aneurysm rebleeding, and SBPV-SD and SBPV-SV, respectively. A *P* value of 0.05 or less was considered statistically significant. All calculations were made with standard commercial software (SPSS Institute, Inc.).

## RESULTS

### Study Population

Baseline characteristics are given in Table 1. The distribution of the study cases and the use of treatment are shown in Figure 1. The overall rebleeding rate was 10.0% (61/612). Of the 47 patients rebleeding within 3 days of ictus, 72.3%

**TABLE 1.** Characteristics of the Patients at Hospital Admission

Characteristics	No., %, of Patients (n = 612)
Age, mean $\pm$ SD, year	53.2 $\pm$ 10.1
Female, n, %	351 (57.4)
Smoking, n, %	236 (38.6)
Sentinel headache, n, %	164 (26.8)
History of hypertension, n, %	356 (58.2)
Hunt-Hess grade, n, %	
1	95 (15.5)
2	217 (35.5)
3	129 (21.1)
4	111 (18.1)
5	60 (9.8)
Fisher grade, n, %	
1	47 (7.7)
2	247 (40.4)
3	205 (33.5)
4	113 (18.5)
aneurysm size, mean $\pm$ SD, mm	7.2 $\pm$ 3.1
No. of aneurysms, n, %	
1	417 (68.1)
2	139 (22.7)
3 or more	56 (9.2)
Aneurysm location, n, %	
ACoA/ACA	190 (31.0)
MCA	124 (20.3)
ICA	239 (39.1)
VBA	59 (9.8)
Seizure at ictus, n, %	81 (13.2)

ACoA/ACA = anterior cerebral communicating artery/anterior cerebral artery, ICA = internal cerebral artery, MCA = middle cerebral artery, MSBP = mean systolic blood pressure, SBPV = systolic blood pressure variability, SD = standard deviation, VBA = vertebrobasilar artery.

underwent clipping, 14.9% underwent coiling, and 12.7% was not treated. Of the 382 controls, 60.5% underwent clipping, 33.5% underwent coiling, and others were early deaths. As a result, the choice of use of treatment was significantly different ( $P < 0.05$ ).

### Systolic Blood Pressure and Rebleeding

Because a complete rest in bed was ordered, few SBP was missing. A total of 66.0% (31/47) cases and 63.4% (242/382) controls received additional antihypertensive treatment ( $P > 0.05$ ). The frequency of additional antihypertensive treatment was  $6.2 \pm 3.2$  in cases and  $5.0 \pm 2.7$  in controls ( $P > 0.05$ ). There was no significant difference between the 2 groups in terms of MSBP ( $P = 0.423$ ). When taking SBPV into consideration, we found that SD of SBP (odds ratio [OR], 3.344; 95% confidence interval [CI], 2.330–4.359;  $P < 0.001$ ) and the SV of SBP (OR, 3.187; 95% CI, 1.923–4.452;  $P < 0.001$ ) were significantly higher in cases (Table 2).

### Other Predictors and Rebleeding

Other univariate baseline predictors of rebleeding included poor Hunt-Hess grade (OR, 4.521; 95% CI, 2.308–8.854;  $P < 0.001$ ), large aneurysm size (OR, 2.953; 95% CI, 1.993–3.913;  $P < 0.001$ ), and seizure at ictus (OR, 2.188; 95% CI,

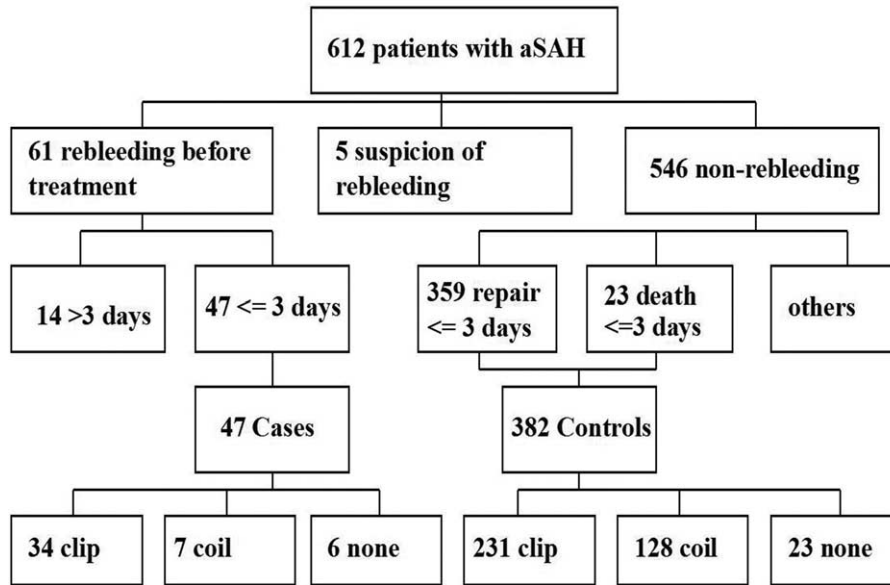


FIGURE 1. The distribution of the study cases and the use of treatment.

1.014–4.719;  $P=0.042$ ). There was a trend for increased rebleeding for patients with sentinel headache ( $P=0.062$ ). And the association between rebleeding and other factors was not significant (Table 2).

**Binary Logistic Regression Analysis**

In a binary logistic regression analysis, high SBPV remained an independent predictor of rebleeding after controlling for large aneurysm size, poor Hunt–Hess grade, seizure at

TABLE 2. Univariate Analysis of Variables as Predictors for Rebleeding

	Rebleeding (n = 47)	No Rebleeding (n = 382)	P Value
Age, mean ± SD, year	55.3 ± 11.5	52.1 ± 10.0	0.397
Female, n, %	26 (55.3)	226 (59.2)	0.640
Smoking, n, %	23 (48.9)	137 (35.9)	0.109
Sentinel headache	20 (42.6)	108 (28.3)	0.062
MSBP, mean ± SD, mm Hg	137.2 ± 20.9	132.1 ± 18.7	0.423
SBPV-SD, mean ± SD, mm Hg	14.3 ± 2.9	10.9 ± 3.4	<0.001
SBPV-SV, mean ± SD, mmHg	16.9 ± 3.8	13.7 ± 4.2	<0.001
Hunt–Hess grade, n, %			<0.001
1 or 2	13 (27.7)	242 (63.4)	
3, 4, or 5	34 (72.3)	140 (36.6)	
Fisher grade, n, %			0.131
1	3 (6.4)	39 (10.2)	
2	15 (31.9)	169 (44.2)	
3	19 (40.4)	97 (25.4)	
4	10 (21.3)	77 (20.2)	
Multiple aneurysms, n, %	11 (23.4)	119 (31.2)	0.275
aneurysm size, mean ± SD, mm	10.5 ± 3.0	7.6 ± 3.2	<0.001
Aneurysm location, n, %			0.871
ACoA/ACA	14 (29.8)	126 (33.0)	
MCA	9 (19.1)	61 (16.0)	
ICA	19 (40.4)	144 (37.7)	
VBA	5 (10.6)	51 (13.4)	
External ventricular drain placed, n, %	18 (38.3)	119 (31.2)	0.321
Seizure at ictus, n, %	10 (21.3)	42 (11.0)	0.042
Time at risk*, mean ± SD, hours	37.2 ± 14.1	39.1 ± 14.4	0.628

ACoA/ACA = anterior cerebral communicating artery/anterior cerebral artery, ICA = internal cerebral artery, MCA = middle cerebral artery, MSBP = mean systolic blood pressure, SBPV = systolic blood pressure variability, SD = standard deviation, VBA = vertebrobasilar artery.

\*Time at risk refers to interval from initial hemorrhage to censoring events which include rebleeding in the case group and aneurysm repair, discharge, or death in the control group.

**TABLE 3.** Adjusted Odds Ratio of Standard Deviation and Successive Variation of Systolic Blood Pressure

	OR	95% CI		P Value
		Lower Limit	Upper Limit	
SBPV-SD	1.254	1.131	1.391	<0.001
SBPV-SV	1.131	1.039	1.231	0.004
Hunt–Hess grade	4.780	2.296	9.950	<0.001
Seizure at ictus	1.819	0.730	4.535	0.199
Sentinel headache	1.695	0.810	3.548	0.161
Aneurysm size	1.156	1.045	1.279	0.005

CI = confidence interval, OR = odds ratio, SBPV = systolic blood pressure variability, SD = standard deviation, SV = successive variation.

ictus, and sentinel headache. The OR was 1.254 (95% CI, 1.131–1.391;  $P < 0.001$ ) for SBPV-SD and 1.131 (95% CI, 1.039–1.231;  $P = 0.004$ ) for SBPV-SV (Table 3, Figure 2).

**OUTCOME**

Overall outcome at 3 month was available for the 429 study patients (Table 4). Patients with rebleeding were more likely to die in the hospital than those who did not experienced rebleeding (OR, 1.236; 95% CI, 1.102–1.385;  $P < 0.001$ ). Also, rebleeding significantly reduced the odds of survival with good outcome (mRS score < 2; OR, 0.424; 95% CI, 0.217–0.829;  $P = 0.009$ ) and reduced the odds of survival with functional independence (mRS score < 4, OR, 0.252, 95% CI, 0.139–0.457;  $P < 0.001$ ).

**DISCUSSION**

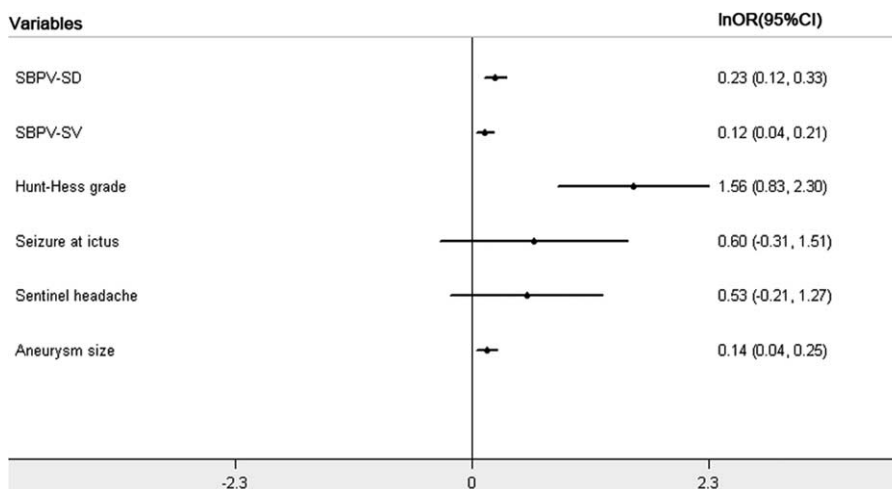
Aneurysm rebleeding is a catastrophic, but preventable complication of SAH, and it is a major cause of in-hospital mortality and morbidity.<sup>3,8</sup> Although most recent studies call for early aneurysm occlusion, rebleeding cannot be completely eliminated.<sup>8,10,11</sup> Recognizing predictors for rebleeding is

essential for identifying the aneurysms that may benefit from acute treatment. However, since then, no consensus about risk factors for rebleeding has been reached.<sup>8,13,14,17,21,22</sup>

In this study, we detected aneurysm rebleeding in 10.0% of all patients with aneurismal SAH. This rate is consistent with previous studies, ranging from 6.9% to 21.5%.<sup>5,11,23</sup> With regard to the risk factors affecting aneurysm rebleeding in acute SAH, our data suggested that large aneurysm size, poor Hunt–Hess grade, and high SBPV were associated with rebleeding, independently of age and gender.

**Large Aneurysm Size**

Most studies confirmed large aneurysm size as a risk factor for rebleeding.<sup>14,22,17</sup> However, some studies revealed that the association between rebleeding and aneurysm size might be confounded by age,<sup>24,25</sup> some found aneurysm diameter was no longer predictive in patients whose aneurysms were repaired within 2 days of admission.<sup>5</sup> As a result, recently Boogaarts et al<sup>15</sup> conducted a meta-analysis and showed that aneurysm size was an important risk factor for aneurysm rebleeding. Consistent with the report, we found that large aneurysm size was a crucial factor for aneurysm rebleeding in acute SAH.



**FIGURE 2.** Forest plot depicting independent relationships between selected clinical variables and aneurysm rebleeding. Confidence intervals that do not cross the line of identity (0) are considered statistically significant. SBPV indicates systolic blood pressure variability. 95%CI = 95% confidence interval, lnOR = Napierian logarithm of odds ratio, SBPV = systolic blood pressure variability, SD = standard deviation, SV = successive variation.

**TABLE 4.** Modified Rankin Scale Score at 3 months, Stratified by Rebleeding

Rankin Scale Score	Rebleeding (n = 47)	No Rebleeding (n = 382)
0 (No symptoms)	1 (2.1)	42 (11.0)
1 (Minor symptoms)	9 (19.1)	115 (30.1)
2 (Some restriction)	2 (4.3)	68 (17.8)
3 (Significant restriction)	2 (4.3)	30 (7.6)
4 (Partly dependent)	1 (2.1)	32 (8.4)
5 (Fully dependent)	7 (14.9)	18 (4.7)
6 (Dead)	25 (53.2)	77 (20.2)

Data are number (percentage) of patients. ( $P < 0.01$ ,  $\chi^2$  test).

### Poor Hunt–Hess Grade

Lord et al<sup>23</sup> found that poor Hunt–Hess grade was significantly associated with aneurysm rebleeding. In particular, Hunt–Hess III, IV, or V was a risk factor for rebleeding. And many other studies supported the association between aneurysm rebleeding and poor clinical condition.<sup>14,17</sup> We also found that patients with Hunt–Hess III, IV, or V tended to experience aneurysm rebleeding in the acute phase of aneurysmal SAH.

### Systolic Blood Pressure

With regard to systolic blood pressure, the 1st major finding of our study was a positive association between SBPV and aneurysm rebleeding within 3 days of ictus. The 2nd major finding was that MSBP did not predict aneurysm rebleeding as expected.

BP variability is an important trigger of vascular events,<sup>26</sup> and SBPV is a powerful predictor of stroke, independently of mean SBP.<sup>27</sup> Along with accompanying reports,<sup>28,29</sup> Rothwell et al<sup>27</sup> believed that these findings challenged the usual blood pressure hypothesis and had implications for diagnosis, treatment, and monitoring of patients with hypertension. Igase et al<sup>30</sup> also showed that the clinical significance of SBPV was higher than that of MSBP with regard to the growth of unruptured intracranial aneurysms. In addition, many reports have demonstrated that SBPV was significantly correlated with cardiac damage, renal dysfunction, and stroke.<sup>31–33</sup> Taken all together, SBPV seems to be a sign of many cardio- and cerebrovascular diseases, which may imply that high SBPV will increase the risk of aneurysm rebleeding. Consistent with this conclusion, our study indicates that high SBPV significantly increases the risk of aneurysm rebleeding in the acute phase. To our knowledge, this is the 1st study about the effect of SBPV on rebleeding in acute SAH. Although PRN antihypertensive treatment may influence SBPV, the frequency of additional antihypertensive treatment is not significantly different between groups in this study. Therefore, this finding implies that controlling the variability of SBP is essential to protect against rebleeding.

With regard to the negative association of MSBP between the 2 groups, our explanation might be that we documented blood pressure values immediately on admission and every 1 hour thereafter, and SBP which was higher than 160 mm Hg would be modified according to the guidelines.<sup>12</sup> As a result, MSBP did not significantly differ from each other in the 2 groups. However, MSBP might increase the risk of aneurysm rebleeding in patients without treatment of SBP. This finding

indicated that the therapeutic effect of modulating high SBP should be considered when investigating the association between MSBP and rebleeding.

Several limitations of our study warrant mention. First, we did not set a standardized protocol and use the same equipment for measuring SBP. SBP values were not recorded by a same researcher, and SBP was taken once per hour which was hard to reflect of second-to-second changes. Second, the amount of time that met the target SBP after antihypertensive therapy was not traceable. Third, the retrospective design would limit the validity of the results. Further prospective studies are required to confirm the relationship between SBPV and rebleeding.

### CONCLUSIONS

SBPV is associated with increased rates of acute aneurysmal rebleeding. Further prospective research is warranted to confirm that SBP stability prevents acute aneurysm rebleeding.

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