The Role of Norepinephrine and Estradiol in the Pathogenesis of Cardiac Wall Motion Abnormality Associated With Subarachnoid Hemorrhage

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Background and Purpose—The majority of patients with ventricular wall motion abnormality (WMA) associated with subarachnoid hemorrhage (SAH) are postmenopausal women. In addition to elevated catecholamine, the role of estrogen in the pathogenesis of WMA has recently been implicated. The objective of this study is to clarify the interrelation among catecholamine, estrogen, and WMA in patients with SAH.

Methods—A retrospective analysis was performed on the medical records of 77 patients with SAH (23 men, 54 women) whose plasma levels of epinephrine, norepinephrine, and estradiol had been measured and echocardiograms had been obtained within 48 hours of SAH onset.

Results—Twenty-four patients (31%) were found to sustain WMA on admission. Multivariate regression analysis revealed that decreased estradiol ($P_{/H11005}=0.018; \text{OR}, 0.902$) and elevated norepinephrine levels ($P_{/H11005}=0.027; \text{OR}, 1.002$) were associated with WMA. After quadrichotomization of 77 patients based on sex/WMA, plasma norepinephrine levels were markedly elevated in men with WMA, whereas estradiol levels were markedly decreased in women with WMA. Plasma norepinephrine and estradiol levels were not correlated. Fifty-four female patients with SAH were further quadrichotomized based on norepinephrine/estradiol levels with a threshold value of 1375 pg/mL for norepinephrine and 11 pg/mL for estradiol. The incidence of WMA in the high-norepinephrine/low-estradiol group was significantly higher than the low-norepinephrine/high-estradiol group.

Conclusions—To our knowledge, this is the first study to evaluate the interrelation among catecholamine, estrogen, and SAH-induced WMA. Lack of estradiol in postmenopausal women may predispose them to develop WMA after poor-grade SAH. However, the precise role of multiple sex hormones in SAH-induced WMA should be evaluated in future prospective studies. (Stroke. 2012;43:1897-1903.)

Key Words: catecholamine □ estrogen □ sex hormones □ subarachnoid hemorrhage □ wall motion abnormality

Patients with aneurysmal subarachnoid hemorrhage (SAH) frequently have complications associated with acute cardiac dysfunctions, which may manifest as arrhythmia, electrocardiographic change, and cardiac wall motion abnormality (WMA).1–15 WMA occurs in patients with SAH with a reported incidence of 8% to 27%.5,7,8 It has been hypothesized that massive release of catecholamine into the systemic circulation after SAH results in the nonischemic usually reversible myocardial injury.1–15 In the cardiology literature, the possible role of estrogen in the pathogenesis of WMA has recently been suggested in patients with takotsubo (stress) cardiomyopathy (TCM).16–18 This hypothesis is based on the clinical observation that a majority of patients with TCM are postmenopausal women, whereas only a few young women are diagnosed with TCM.16,17 However, whether estrogen plays a major role in the pathogenesis of SAH-induced WMA has never been previously investigated. It is probable that decreased estrogen levels are causally associated with WMA in patients with SAH, because SAH-induced WMA also occurs more frequently in postmenopausal women with poor-grade SAH.1–15 In our institution, plasma catecholamine (epinephrine/norepinephrine) and estradiol levels are measured and transthoracic echocardiogram (TTE) is routinely performed in patients with SAH shortly after admission. This study was conducted to clarify the role of catecholamine and estrogen in the pathogenesis of SAH-induced WMA. Because catecholamine in the systemic circulation is rapidly metabolized and its plasma level decreases with time, we focused only on patients from whom blood samples were obtained within 48 hours of SAH onset. Moreover, only those whose

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sample was collected before therapeutic intervention to obliterate an aneurysm were included to minimize the influence of the intervention.

Subjects and Methods

Study Population

Between April 2007 and November 2010, a total of 290 patients with aneurysmal SAH were admitted to our institution, which is a tertiary referral center for stroke. Plasma catecholamine/estradiol measurement and TTE were conducted in 147 patients (51%). Fifty-six patients were excluded from this analysis because either blood sample collection or TTE had not been completed within 48 hours of SAH onset. Patients with severe hypotension who had received inotropic agents before blood sample collection (n=6), those who had previously undergone cardiac arterial bypass graft surgery (n=3), and those who had received oral estrogen as supplement therapy or antiandrogen/aromatase inhibitors as chemotherapy for cancer (n=3) were also excluded. As a result, 77 of the 290 patients with SAH (27%) were included in this retrospective study. Demographic data and outcomes of these 77 patients were retrieved by reviewing medical charts, radiographic images, and the institutional database. The study protocol was approved by our institution’s internal review board, and informed consents were obtained from family members or patients’ relatives.

TTE Evaluation

All 77 patients underwent bedside 2-dimensional TTE using a General Electric Vivid 7 (GE Healthcare, Tokyo, Japan) in either the emergency department or the neurosurgical intensive care unit. Experienced ultrasound technicians performed the TTE procedure, and the following images were routinely obtained: parasternal long axis; parasternal short axis at the level of the mitral valve, papillary muscles, and apex; apical 2-, 3-, and 4-chamber; subcostal 4-chamber; and subcostal short axis. The American Society of Echocardiography’s 16-segment model and regional wall motion score index were used for analyzing WMA. Regional wall motion score index in WMA was calculated by averaging the scores for all 16 segments, and WMA was defined as a regional wall motion score index ≥1.0. Cardiac function was represented by left ventricular ejection fraction. All TTE studies were interpreted by a board-certified cardiologist who was unfamiliar with the patient or details of the clinical scenario.

Plasma Catecholamine/Estradiol Measurement

By inclusion criteria, all 77 patients had blood samples drawn within 48 hours of SAH onset. In addition to routine complete blood count and blood chemistries panels, plasma levels of epinephrine and norepinephrine were measured with high-performance liquid chromatography (SRL Inc., Tokyo, Japan). Plasma levels of estradiol were measured at a central laboratory by the electrochemiluminescence immunoassay method (SRL Inc.). In addition, serum level of troponin I, a marker for acute myocardial injury, was measured using a standard chemiluminescence immunoassay.

Clinical Management

All patients with SAH underwent either surgical or endovascular obliteration of an aneurysm within 48 hours of SAH onset unless their systemic or neurological condition was considered unfit for vigorous treatment. Postoperative management included placement of a spinal catheter to evacuate subarachnoid clot, the use of intravenous fasudil hydrochloride (Mitsubishi-Tanabe Pharma, Osaka, Japan), and low-molecular weight dextran and albumin to attenuate vasospasm. Central venous catheters were placed routinely to monitor central venous pressure, although pulmonary artery catheters were seldom placed. For patients with symptomatic vasospasm, triple-H therapy was initiated. However, for patients with cardiopulmonary compromise, effort was made to keep them normovolemic instead of hypervolemic to avoid its exacerbation. Patients underwent brain CT routinely on the 14th day after aneurysmal obliteration to evaluate the presence and extent of delayed cerebral infarction associated with vasospasm.

Statistical Analysis

For comparison of demographic variables between patients with and without WMA, Fisher exact test was used for categorical variables and unpaired t test for continuous variables. Multivariate regression analysis was used to identify clinical variables that were correlated with WMA. The 77 patients were quadrichotomized into 4 groups based on sex and the presence of WMA: men with WMA, men without WMA, women with WMA, and women without WMA. Plasma levels of norepinephrine and estradiol were compared among the 4 groups by 1-way analysis of variance with Bonferroni correction. Linear regression analysis was used to evaluate the relationship between plasma norepinephrine and estradiol levels. The receiver operating characteristics curves were created for plasma norepinephrine and estradiol levels. From the receiver operating characteristics curve, we derived optimal threshold values to distinguish between patients with and without WMA by seeking the best tradeoff between highest possible sensitivities and specificities of the threshold values. JMP (SAS Institute, Cary, NC) was used for statistical analysis. Data are indicated by mean±SE, and P<0.05 was considered statistically significant.

Results

Demographics and Outcomes

The 77 ethnic Japanese patients with SAH comprised 23 men and 54 women. Their ages ranged from 35 to 90 years (mean, 62.8±12.5 years). Twenty-four patients (31%) were found to sustain WMA on admission with a frequency of 22% in men and 36% in women. The frequency was not significantly different (P=0.29). The interval between SAH onset and completion of TTE/blood sample collection ranged from 2 to 48 hours (mean, 17.7±12.8 hours). Comparison of demographic and physiological variables, summarized in Table 1, revealed that the WMA+ group was significantly more severe with regard to SAH grade than the WMA− group. Cardiac damage was more severe in the WMA+ group as represented by significantly higher plasma troponin I level (0.76±0.21 ng/mL versus 0.11±0.13 ng/mL; P=0.01), higher frequency of electrocardiographic abnormalities (100% versus 72%; P=0.004), and lower left ventricular ejection fraction (49.9%±8.7% versus 68.6%±12.5%; P<0.001). Regional wall motion score index in WMA+ group ranged from 1.05 to 2.10 (mean, 1.80±0.29). The interval between SAH onset and completion of TTE/blood sample collection ranged from 2 to 48 hours (mean, 17.7±12.8 hours). Comparison of demographic and physiological variables, summarized in Table 1, revealed that the WMA+ group was significantly more severe with regard to SAH grade than the WMA− group. Cardiac damage was more severe in the WMA+ group as represented by significantly higher plasma troponin I level (0.76±0.21 ng/mL versus 0.11±0.13 ng/mL; P=0.01), higher frequency of electrocardiographic abnormalities (100% versus 72%; P=0.004), and lower left ventricular ejection fraction (49.9%±8.7% versus 68.6%±12.5%; P<0.001). Regional wall motion score index in WMA+ group ranged from 1.05 to 2.10 (mean, 1.80±0.29; Table 1). Although vital signs were stable in majority of WMA− patients, 8 patients (33%) developed pulmonary edema, and the frequency was also significantly higher in the WMA+ group. Although age, frequency of ruptured posterior circulation aneurysm, and frequency of cardiac arrhythmia tended to be higher in the WMA- group, the difference was not statistically significant. There was no significant intergroup difference in systolic blood pressure on admission. The inpatient mortality rate was significantly higher in the WMA+ group (54% versus 9%; P<0.001). The frequency of cerebral infarction associated with vasospasm, evaluated with a brain CT obtained on the 14th day after SAH onset, was also significantly higher in the WMA+ group (47% versus 18%; P=0.04).

Multivariate Regression Analysis

Clinical variables evaluated included age, sex, SAH grading according to the World Federation of Neurosurgical Societies
scale, location of ruptured aneurysm (anterior versus posterior circulation), and plasma levels of epinephrine, norepinephrine, and estradiol. Multivariate regression analysis showed that decreased estradiol ($P=0.018$; OR, 0.902) and increased norepinephrine levels ($P=0.027$; OR, 1.002) were correlated with WMA (Table 2). WMA was significantly less likely to occur in good-grade SAH (World Federation of Neurosurgical Societies Grade I–III; $P=0.049$; OR, 0.220). Age, sex, location of aneurysm, and plasma epinephrine levels were not correlated with WMA (Table 2).

### Table 2. Multivariate Regression Analysis to Identify Clinical Variables Associated With Wall Motion Abnormality in Patients With Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Clinical Variables</th>
<th>OR</th>
<th>95 % CI</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.012</td>
<td>0.949–1.079</td>
<td>0.713</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.274</td>
<td>0.037–2.053</td>
<td>0.208</td>
</tr>
<tr>
<td>WFNS Grade I–III SAH</td>
<td>0.220</td>
<td>0.048–0.998</td>
<td>0.049*</td>
</tr>
<tr>
<td>Anterior circulation aneurysm</td>
<td>0.207</td>
<td>0.020–2.167</td>
<td>0.189</td>
</tr>
<tr>
<td>Epinephrine, pg/mL</td>
<td>1.004</td>
<td>0.998–1.009</td>
<td>0.167</td>
</tr>
<tr>
<td>Norepinephrine, pg/mL</td>
<td>1.002</td>
<td>1.001–1.003</td>
<td>0.027*</td>
</tr>
<tr>
<td>Estradiol, pg/mL</td>
<td>0.902</td>
<td>0.887–0.980</td>
<td>0.018*</td>
</tr>
</tbody>
</table>

*WFNS indicates World Federation of Neurological Societies; SAH, subarachnoid hemorrhage.

**Sex, WMA, and Norepinephrine Levels**

Plasma norepinephrine levels (normal, 150–330 pg/mL in resting state) were compared among men with WMA (n=17), men without WMA (n=18), women with WMA (n=19), and women without WMA (n=35; Figure 1A). The levels in men with WMA (2977.8±450.0 pg/mL) were significantly higher than those in men without WMA (1042.2±237.1 pg/mL; $P<0.001$), women with WMA (1530.4±230.8 pg/mL; $P<0.001$), and women without WMA (650.6±170.1 pg/mL; $P<0.0001$). The levels in women with WMA were significantly higher than those in women without WMA ($P<0.001$; Figure 1A).

**Sex, WMA, and Estradiol Levels**

Similarly, plasma estradiol levels (normal, 10–82 pg/mL for Japanese men and 14–17 pg/mL for Japanese postmenopausal women) were compared among the 4 groups (Figure 1B). The levels in women without WMA (15.8±1.9 pg/mL) were significantly higher than those in women with WMA (7.7±2.6 pg/mL; $P=0.02$). The levels in men without WMA (18.8±2.7 pg/mL) were significantly higher than those in women with WMA ($P=0.002$). However, the levels in men with WMA (17.2±5.1 pg/mL) were not significantly different than those in men without WMA ($P=0.79$; Figure 1B).
Relationship between plasma NE and E2 in SAH patients

A: women; B: men

\[ y = -5.46x + 1052.8 \]
\[ R = -0.02 \]
\[ p = 0.63 \]

\[ y = 2.34x + 992.4 \]
\[ R = 0.14 \]
\[ p = 0.52 \]

Figure 2. Linear regression analysis revealed that there was no correlation between plasma norepinephrine and estradiol levels in the 54 female patients \((R = -0.02, P = 0.63; A)\) and in the 23 male patients \((R = 0.14, P = 0.52; B)\).

Relationship Between Norepinephrine and Estradiol

Linear regression analysis revealed that there was no correlation between plasma levels of norepinephrine and estradiol in the 54 female patients \((R = -0.02, P = 0.63; Figure 2A)\). Similarly, there was no correlation between plasma levels of norepinephrine and estradiol in the 23 male patients \((R = 0.14, P = 0.52; Figure 2B)\).

Relationship Among WMA, Norepinephrine, and Estradiol

In the 54 female patients, the threshold values for WMA determined by receiver operating characteristics curves were 1375 pg/mL for norepinephrine (Figure 3A) and 11 pg/mL for estradiol, respectively (Figure 3B). The area under the curve was 0.67 for norepinephrine and 0.68 for estradiol (Figure 3A–B). All female patients were further quadrichotomized according to the calculated values (Figure 4): high-estradiol/low-norepinephrine (upper left, n=11; mean age, 59.5±14.7 years), high-estradiol/high-norepinephrine (upper right, n=7; mean age, 62.0±13.7 years), low-estradiol/high-norepinephrine (lower right, n=9; mean age, 70.1±12.2 years), and low-estradiol/low-norepinephrine (lower left, n=27; mean age, 67.7±10.8 years). The incidence of WMA in the high-estradiol/low-norepinephrine group was significantly lower than that in the low-estradiol/high-norepinephrine group (18% versus 78%; \(P = 0.02; Figure 4)\). The former group was also significantly younger than the latter (59.5±14.7 years versus 70.1±12.2 years; \(P < 0.05\)). Similarly, the receiver operating characteristics curves were created for the 23 male patients. Although elevated plasma norepinephrine level (>2008 pg/mL) was marginally correlated with WMA in men \((P = 0.06; Figure 3C)\), decreased estradiol level (<15 pg/mL) was not correlated with WMA \((P = 0.50; Figure 3D)\). Therefore, quadrichotomization among male patients was not performed.

Discussion

Cardiac wall motion abnormality occurs relatively frequently after SAH with a reported incidence of 8% to 27%. Poor-grade SAH, advanced age, and female sex seem to be risk factors for WMA. In other words, elderly women with poor-grade SAH are most likely to sustain WMA. Although excessive release of catecholamine, predominantly norepinephrine, into the systemic circulation caused by over-activation of the sympathetic nerve terminals after SAH has been implicated as the principal trigger of SAH-induced WMA, the “catecholamine surge hypothesis” alone does not explain why SAH-induced WMA occurs very rarely in young women and men. This argument has led to another hypothesis that estrogen also plays an important role in the pathogenesis of WMA, particularly in patients with TCM. However, plasma estrogen levels have rarely been measured either in patients with TCM or in those with neurogenic WMA. In this context, this is the first clinical study that systematically evaluated the interrelationship among catecholamine, estrogen, and WMA in patients with SAH.

Obviously, the degree of cardiac damage was more severe in the WMA+ group as represented by the significantly higher plasma troponin I level, higher frequency of electrocardiographic abnormalities, and lower left ventricular ejection fraction (Table 1). The frequency of pulmonary edema was also significantly higher in the WMA+ group. Interestingly, no patients in the WMA− group developed pulmonary edema. The worse outcomes for the WMA+ group, as represented by the higher inpatient mortality rate and higher frequency of cerebral infarction associated with vasospasm (Table 1), may be attributable both to the worse initial SAH grade and cardiac dysfunction in the former. Although WMA in some patients with SAH might have been incidental, the mean regional wall motion score index of 1.80±0.40 (Table 1) suggests that the degree of WMA was substantial in most of them.

The results of multivariate regression analysis show that SAH grading, increased plasma norepinephrine, and decreased plasma estradiol levels were independently associated with WMA (Table 2). There was no correlation between plasma norepinephrine and estradiol levels in either sex (Figure 3A–B). A combination of increased norepinephrine and decreased estradiol levels seems to predict WMA reliably in female patients with SAH (Figure 4). Interestingly, neither high norepinephrine levels in the presence of high estradiol nor low estradiol levels in the presence of low norepinephrine were associated with elevated incidence of WMA. These results are in concordance with those in the literature and seem to explain why WMA develops most frequently in postmenopausal women with poor-grade SAH. Although this retrospective study does not provide clues to the mechanism...
of possible cardiac protection by estrogen, there is much circumstantial evidence to support current results. Clinically, supplementary estrogen has been shown to protect the cardiovascular system from the adverse effects of elevated norepinephrine.17,23,24 Experimentally, estrogen supplementation in ovariectomized female rats led to the upregulation of cardioprotective substances such as heat shock protein 70 and atrial natriuretic peptide,18,25 and reduction in c-fos

Figure 3. The receiver operating characteristics (ROC) curves were created for both plasma norepinephrine (NE) and estradiol (E2) levels. From the ROC curve, optimal threshold values to distinguish between patients with and without wall motion abnormality were derived. In women, the threshold values were 1375 pg/mL for NE (A) and 11 pg/mL for E2 (B). The area under the curve (AUC) was 0.67 for NE (A) and 0.66 for E2 (B). In men, the threshold values were 2008 pg/mL for NE (C) and 15 pg/mL for E2 (D). The AUC was 0.83 for NE (C) and 0.61 for E2 (D).

Figure 4. The 54 female patients with SAH were quadrichotomized according to their plasma norepinephrine (NE)/estradiol (E2) levels. The incidence of WMA in the high-estradiol/low-norepinephrine group (upper left) was significantly lower than that in the low-estradiol/high-norepinephrine group (lower right). SAH indicates subarachnoid hemorrhage; WMA, wall motion abnormality.
mRNA,18,25 which promotes hypertrophy and apoptosis of the cardiac muscle after translation.26 This study is also unique because all patients were of single ethnicity, that is, native Japanese. Plasma estradiol levels are known to vary substantially by ethnicity, and the results might have been different in other countries with multiethnic populations.19,22,27

According to the results of demographic comparison (Table 1) and multivariate regression analysis (Table 2), men are less likely to develop WMA than women, although the sex difference was not statistically significant. The threshold value for norepinephrine also seems to be higher in men than women (Figure 3C). Figure 2A shows that men with WMA exhibited significantly higher levels of norepinephrine than men without WMA. In contrast, there was no significant difference in estradiol levels between the 2 groups (Figure 2B). Taken together, these results suggest that is highly elevated norepinephrine levels rather than decreased estradiol levels may be responsible for SAH-induced WMA in men. It is possible that male patients with SAH may be protected from WMA by the dual presence of androgen and estrogen. The measurement of plasma androgen levels in patients with SAH was not performed in this study, however, and the hypothesis has to be verified by a prospective study of multiple sex hormone levels and WMA after SAH.

This study has also highlighted a possible pathogenic difference between SAH-induced WMA and TCM. Although both conditions exhibit similar clinical and echographical profiles, there is controversy surrounding whether they are identical.28 The results of this study suggest that the 2 conditions may not be identical in pathophysiological terms: although elevation in norepinephrine rather than epinephrine levels is primarily responsible for SAH-induced WMA as shown in this study as well as in the literature,29,30 elevation of both epinephrine and norepinephrine seems to be responsible in TCM.31 The possibility that increased afterload after norepinephrine-induced peripheral vasoconstriction is responsible for WMA in patients with SAH cannot be excluded, because pulmonary artery catheters were rarely placed. Confirmation of whether this speculation is correct requires further accumulation of experimental and clinical data.

There are several limitations to this study. First, the study design is retrospective and only 27% of total patients with SAH were included. Second, plasma catecholamine released into the systemic circulation after SAH is rapidly degraded and plasma levels decrease over time.30,32 We attempted to reduce such time-related variability by our strict inclusion criteria (ie, including only patients in whom TTE and blood sample collection had been conducted within 48 hours of SAH onset). Nevertheless, the possibility that the difference in the timing of sample collection may have influenced measurement results cannot be denied. Third, 6 patients with severe hemodynamic compromise requiring the use of intravenous vasopressors were excluded from analysis because plasma catecholamine levels had already been affected substantially by their use. It is possible that intrinsic plasma catecholamine levels are particularly elevated in that group and therefore the actual difference between the WMA− and WMA+ groups might have been greater. Fourth, the accuracy of the quadrichotomized table based on a combination of norepinephrine and estradiol levels (Figure 4) may not be optimal considering the relatively low area under the curve values (Figure 3A–B).

Despite such shortcomings, to our knowledge, this study is the first to evaluate the interrelationship among catecholamine, estradiol, and WMA in patients with SAH, and we believe that it will provide new insight into the pathogenesis of SAH-induced WMA. This study may also have therapeutic implication: it may be worth considering the administration of estradiol to postmenopausal female patients with SAH with the complications of severe WMA.

**Conclusion**

SAH-induced WMA appears to be influenced by plasma norepinephrine and estradiol levels. Particularly in women, the combination of elevated norepinephrine and reduced estradiol levels is associated with WMA. In men, SAH-induced WMA may occur only when plasma norepinephrine levels are exceedingly high. Whether sex hormones have a cardioprotective role against SAH-induced massive catecholamine release needs to be evaluated further in future prospective studies.

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**Disclosures**

None.

**References**


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