Effect of Age on Cerebral Blood Flow Velocity and Incidence of Vasospasm After Aneurysmal Subarachnoid Hemorrhage

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Background and Purpose—Current transcranial Doppler criteria for vasospasm after aneurysmal subarachnoid hemorrhage are not age specific. We analyzed the effect of age on cerebral blood flow velocity changes after subarachnoid hemorrhage and constructed an age-adjusted predictive model of cerebral blood flow velocity in subarachnoid hemorrhage patients.

Methods—We identified patients with aneurysmal subarachnoid hemorrhage admitted between 1991 and 1999 with a prospective transcranial Doppler database. Eighty-one patients, with complete medical records and transcranial Doppler examinations of the vessels of interest, were included. Patients were subdivided into 2 groups by age: younger, <68 years of age (n=47) and older, ≥68 years of age (n=34). Maximum mean flow velocity and incidence of symptomatic vasospasm were reported. Linear and nonlinear regression analyses were performed.

Results—Middle cerebral artery and internal carotid artery mean flow velocity were lower in older patients (median 76 versus 114 cm/s and 76 versus 126 cm/s, respectively; P<0.003). Incidence of symptomatic vasospasm was lower in older patients (44% versus 66%; P=0.05). Older patients developed symptomatic vasospasm at lower middle cerebral artery (median 57 versus 103 cm/s; P=0.04) and internal carotid artery (median 54 versus 81 cm/s, P=0.02) mean flow velocity. Relationship between middle cerebral artery and internal carotid artery mean flow velocity and age was quadratic (ANOVA, P<0.0001).

Conclusions—Older patients have a lower incidence of symptomatic vasospasm, and such vasospasm develops at lower cerebral blood flow velocity than younger patients. A quadratic relationship was found between age and cerebral blood flow velocity. This model could be used to create an age-adjusted nomogram that might improve diagnostic capabilities of transcranial Doppler. (Stroke. 2001;32:2005-2011.)

Key Words: aging ■ cerebral angiography ■ subarachnoid hemorrhage ■ ultrasonography, Doppler, transcranial ■ vasospasm

Cerebral angiography remains the gold standard for diagnosis of cerebral vasospasm (VSP). Since the introduction of transcranial Doppler (TCD), various authors have reported on its usefulness as a noninvasive measurement of cerebral blood flow velocity (CBFV) within the circle of Willis for the evaluation of VSP in patients after aneurysmal subarachnoid hemorrhage (SAH). Currently patients are reported to have transcranial Doppler–defined VSP if CBFV is above a threshold velocity. This threshold varies among studies, even those pertaining to the same vessel. Sensitivity of TCD for detection of angiographic VSP in the middle cerebral artery (MCA) ranges from 39% to 85%

With advancing age, a decrease in CBFV and a concomitant increase in indexes of peripheral resistance are found in all vessels. These findings are more pronounced in subjects of age >40 years. Current criteria for TCD-defined VSP are based predominantly on CBFV in younger patients without adjusting for factors such as age and days after SAH, which potentially limits their predictive power in older patients. Various studies have mentioned the effect of age on CBFV after SAH. Only 1 study described a negative linear correlation between measured MCA maximum mean flow velocity (MMFV) and age (r=−0.525, P<0.01) in SAH patients. Data-driven age-adjusted criteria may improve diagnostic capabilities of TCD.

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The aim of this retrospective analysis is to determine the effect of age after SAH on (1) time profile of changes in TCD measured CBFV and (2) incidence of VSP. A secondary aim is to construct an age-adjusted predictive model of CBFV in SAH.

Subjects and Methods

Patients

We evaluated retrospectively all patients admitted to the Neurosciences Critical Care Unit with the diagnosis of aneurysmal SAH between 1991 and 1999. Patients were identified using a prospective TCD database maintained in the Neurosciences Critical Care Unit. Patients with traumatic and nonaneurysmal SAH were excluded. We reviewed medical records of all patients and collated data regarding demographic characteristics, clinical presentation, location of aneurysm, Fisher grade,13 Hunt and Hess score,14 and symptomatic VSP. Onset of SAH was presumed to be at headache onset.

Symptomatic VSP

Diagnosis of symptomatic VSP was based on onset of new focal or global neurological deficit not explained by hydrocephalus, hemorrhage, surgical complications, fever, infections, or metabolic abnormalities. Retrospective diagnosis was not attempted and was considered only (1) if made during the patient’s hospital stay and (2) if symptoms resolved after either hypervolemic-hypertensive or endovascular therapy.

TCD Ultrasonography

MFV of the anterior circulation vessels was recorded in centimeters per second by a 2-MHz transducer (CDS, Medasonics; Intraview, RIMED) by use of a transtemporal approach. All vessels were insonated according to the method described by Aaslid et al.1 Because it was shown that most patients with anterior circulation aneurysms who develop VSP have involvement of the basal arteries15 and absence of accurate interdependence between VSP symptoms and actual arterial territory involved,16,17 our analysis was restricted to the M1 segment of the MCA and the C1 segment of the internal carotid artery (ICA) insonation. In addition, insonation of the MCA and of ICA segment C1 is more accurate and reproducible4,18 than of the ACA.2,5 We report MFV of the right M1 and left ICA segment C1. If the patient developed focal symptoms, we reported MFV of the side correlating with the symptoms.

Lindegaard ratio also was calculated to differentiate between hyperemia and VSP.19 Patients were reported to have TCD VSP when mean MFV was ≥100 cm/s20 and Lindegaard ratio was >3.19 We reported the following: (1) Gosling pulsatility index (PI);21 and maximum MFV (MMFV); (2) baseline MFV defined as velocities recorded on the first 2 days of admission; (3) percentage change in MFV, defined as the difference between MMFV and baseline MFV divided by the baseline MFV; and (4) proportion of patients with ≥50-cm/s increase in MFV per 24 hours.22 Length of the period between recording MMFV and diagnosis of symptomatic VSP was calculated.

Cerebral Angiography

Cerebral angiograms obtained during the patient’s hospital stay were interpreted by a neuroradiologist and compared with those performed on admission. We defined angiographic VSP as a vessel lumen diameter reduction ≥51% because of the strong correlation between >50% reduction in vessel diameter and ischemic reduction in regional cerebral blood flow.23

Statistical Analysis

We analyzed data using SPSS 10.0 statistical software package (SPSS Inc). Patient characteristics were summarized with frequency distributions, means, SEMs, median, range, and percentiles as appropriate. Pearson $\chi^2$ was calculated for $2 \times 2$ tables. Fisher’s Exact Test was computed when tables had cells with an expected frequency of <5. A matrix scatterplot was created to examine the data and determine the best age to dichotomize patients. Nonparametric Mann-Whitney or Wilcoxon rank sum tests were used to compare groups. Linear and nonlinear regression analyses were performed to detect a correlation between age and CBFV. For each model, regression coefficients, $R^2$, SEE, predicted values, and residuals were calculated. Contingency tables (2×2) were constructed to calculate sensitivity and specificity of TCD for detecting symptomatic VSP. A $P$ value <0.05 was considered significant.

Results

Demographic Data

We identified 311 patients with SAH. Of those, 25 had a traumatic SAH and 83 had an aneurysmal SAH. Only 81 of 203 (40%) had complete medical records and TCD examinations that included the vessels of interest (619 TCD studies were reviewed). Median patient age was 62 years (range 21 to 84 years); 75% were women. On presentation to the hospital, 41% had mild headache (Hunt and Hess score 1) and 4% were comatose (Hunt and Hess score 5). Forty-two percent had diffuse SAH on CT scan of the head (Fisher grade 2). Most of the aneurysms were in the anterior circulation (94%), of which 44% were anterior communicating artery aneurysms. Mean time to surgical or endovascular intervention was 2 days. A total of 90% (73 of 81) of the patients underwent clipping, and 8% (6 of 81) underwent endovascular coiling. One patient had no intervention, and both clipping and coiling was performed on another.

Scatterplot of CBFV by age (Figure 1) demonstrated a sharper decline in CBFV for patients ≥68 years of age. This finding led us to dichotomize patients into 2 age groups: younger (n=47), defined as age <68 years; and older, (n=34) defined as age ≥68 years. No difference was seen between groups in relation to race, sex, Glasgow coma scale score, Hunt and Hess score and Fisher grade, aneurysm location, or type of vascular intervention performed.

Effect of Age on CBFV and PI

Older patients had a significantly lower baseline MFV and MMFV in both MCA and ICA. Table 1 illustrates the effect
of age on MCA and ICA MFV. The number of days to MMFV was not significantly different between the 2 age groups. A total of 50% of patients reached MMFV on day 7 of SAH. We found a similar percentage change from baseline to MMFV in older and younger patients. We noted a trend toward a faster rise in MFV in younger patients. A total of 30% of younger patients versus 15% of older patients had MFV rise $\geq 50$ cm/s per 24 hours ($P=0.07$). We found a significantly higher proportion of younger patients with MMFV $\geq 160$ cm/s ($P=0.05$). Conversely, a higher proportion of older patients have MMFV $< 80$ cm/s ($P=0.05$).

We found a significant increase in PI with advancing age. The MCA PI was 0.88 in younger and 1.09 in older patients ($P=0.0005$). Similarly, ICA PI was 0.86 in younger and 1.2 in older patients ($P=0.0005$).

Effect of Age on Diagnosis of VSP

The most common presentation of symptomatic VSP in our study was confusion (66.7% in older and 55.6% in younger patients). Focal symptoms were found in 13.3% of older patients and 13% of younger patients. No significant difference was found in the presenting symptoms of VSP between older and younger patients. Older patients had a lower incidence and earlier onset of symptomatic VSP (Table 2) and developed symptomatic VSP at lower CBFV. Median time to symptomatic VSP was 5 and 7 days after SAH in older and younger patients, respectively ($P=0.06$). MMFV preceded diagnosis of symptomatic VSP by 2 days in older and 1 day in younger patients ($P=0.7$). A Kaplan-Meier curve (Figure 2) demonstrated that none of the older patients developed symptomatic VSP after day 10 following SAH, whereas younger patients continued to develop symptomatic VSP until day 16.

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<th>TABLE 1. Effect of Age on MCA and ICA Velocity</th>
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<tr>
<td>Age, y</td>
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<td>Baseline MFV, cm/s, mean (SE)</td>
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<td>MCA</td>
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<td>Time to MMFV, d, median (range)</td>
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<td>MMVF $&gt; 160$ cm/s, n (%)</td>
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<td>MMFV $&lt; 80$ cm/s, n (%)</td>
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<td>%ΔMFV, mean (SE)</td>
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<td>MFV increase $\geq 50$ cm/s per 24 h, n (%)</td>
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<th>TABLE 2. Effect of Age on VSP</th>
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<td>Age, y</td>
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<td>Symptomatic VSP, n (%)</td>
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<td>Time to symptomatic VSP, median (range), d</td>
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<td>VSP MCA MFV, cm/s</td>
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<td>TCD VSP, %</td>
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<td>Angiographically confirmed TCD VSP, n (%)</td>
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<td>Radiological VSP, n (%)</td>
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Incidence of TCD-defined VSP was significantly higher in younger (42%) versus older (23%) patients ($P<0.0001$). Only 36 (44%) patients had cerebral angiograms performed as follow up or for possible VSP. Incidence of radiological VSP was 74% in younger and 47% in older patients ($P<0.1$).

Twenty-eight patients (35%) underwent TCD and angiographic studies on the same day symptomatic VSP was suspected. The incidence of angiographically confirmed TCD VSP was 53% in younger patients and 33% in older patients ($P<0.2$).

Effect of Age on TCD Sensitivity and Specificity: Sensitivity and Specificity of TCD to Detect Symptomatic VSP Varied With Age

For the MCA, TCD sensitivity was higher in younger (60%) versus older (38%) patients. Conversely, specificity was higher in older (77%) compared with younger (58%) patients. For the ICA, TCD sensitivity was higher in younger (42.9%) compared with older (20%) patients; specificity was not different between groups (80%).

Regression Analysis

To analyze the age-related decline of MFV in the MCA and ICA, linear and quadratic regression models were constructed. Models are described in formulas 1 through 4. We entered the following variables into the model: (1) age, (2) SAH day (PSAHD), (3) SAH day category (SAHDC), and (4) clinical spasm (CSPASM). The variable SAHDC was introduced into the model to emphasize the change in CBFV seen late in the course of SAH. SAHDC was defined as 0 if SAH day was $\leq 12$ and PSAHD-12 if SAH day was $>12$. CSPASM was defined as 0 when VSP was absent and “1” when VSP was present.

The MCA linear model equation is as follows.

$$MFV = 105.28 - 0.67 \text{Age} + 2.63 \text{PSAHD} - 4.99 \text{SAHDC} + 13.81 \text{CSPASM}$$

The MCA quadratic model equation is as follows.

$$MFV = 52.6 + 1.3 \text{Age} - 0.017 \text{Age}^2 + 2.65 \text{PSAHD} - 5.05 \text{SAHDC} + 14.5 \text{CSPASM}$$

The ICA linear model equation is as follows.

$$MFV = 73.88 - 0.28 \text{Age} + 2.99 \text{PSAHD} - 8.14 \text{SAHDC} + 13.24 \text{CSPASM}$$

The ICA quadratic model equation is as follows.

$$MFV = 96.37 - 1.12 \text{Age} + 0.007 \text{Age}^2 + 2.97 \text{PSAHD} - 8.08 \text{SAHDC} + 12.95 \text{CSPASM}$$

The quadratic model fit the data best for both MCA ($R^2=0.14$, $P<0.0001$) and ICA ($R^2=0.093$, $P<0.0001$; Figure 3). In the MCA, most of the decline in MFV occurred in older patients. The slope of this MFV decline is 9-fold in patients of age $\geq 68$ versus $<68$ years. As for the ICA, most of the decline was in the younger patients. The slope of the decline is 8-fold in patients of age $<68$ versus $\geq 68$ years.

Discussion

Results of the present study provide new insights into the effect of aging on CBFV in patients after aneurysmal SAH. First, we have shown that older SAH patients have lower MMFV and baseline MFV. Second, older patients developed symptomatic VSP at normal-range MFV. Third, older patients may have a shorter high-risk period to development of symptomatic VSP. Finally, the age-related decline in CBFV was not linear but instead was quadratic, and the slope of this decline varied with the type of vessel insonated.

Effect of age on CBFV and PI

Age-related decline in CBFV has been reported in previous studies. Although these studies clearly demonstrated an
inverse relationship between age and CBFV, a small sample size of patients >60 years of age did not allow the authors to perform multivariate logistic regression analysis and adjust for factors such as SAH day and presence of symptomatic VSP. The decline in CBFV with age may be associated with certain changes in cerebrovascular hemodynamics such as (1) decreased CBF or metabolic demands, (2) vessel-size changes, and (3) lower cardiac output.

Aging is associated with a 20% to 30% decrease in CBF in healthy individuals between the ages of 20 and 80 years. Several authors have examined the relationship between relative changes in CBFV and changes in CBF in normal subjects. A linear relationship has been reported between CBFV and the mean cerebral transit time of Tc and between percentage change in MCA MFV and percentage change in CBF. Although the linear relationships found in these studies do not meet the criterion of having a slope of 1 and a y intercept of 0, they suggest that changes in CBFV reflect changes in CBF.

Aging is also associated with dilatation of major extracranial arteries and reduction of flow within parenchymal vessels. Kusunoki et al demonstrated poor visibility of the intracerebral ICA and M1 segment of the MCA on magnetic resonance angiography secondary to progressive kinking, elongation, and stenosis with advancing age.

Several authors have examined the effect of aging on the cardiovascular system. These studies demonstrate an age-related prolongation of isovolumic cardiac relaxation, which results in reduced efficacy of early ventricular diastolic filling and an age-related drop in cardiac index.

In the present study, along with a decrease in CBFV with advancing age comes an increase in PI. This may be secondary to age-related stiffening of the arteries, which often dilate and become tortuous. The more-elastic (younger) vessels damp the pulse and pressure wave more effectively than do stiff, aged vessels. Thus, aging increases the systolic-diastolic pressure ratio, which results in an increase in PI.

Effect of Age on VSP

VSP remains a major complication associated with aneurysmal SAH that results in delayed ischemic deficits in 2% to 24% of all cases. Our symptomatic VSP incidence was higher compared with Boecher-Schwarz et al. They reported a 23% incidence of VSP in patients <55 and 0% in patients >55 years of age. Higher incidence of symptomatic VSP in our series is probably secondary to a higher degree of severity of SAH. Of our patients, 42% had a Hunt and Hess score ≥3 on admission, compared with 25% in the Boecher-Schwarz series.

Incidence of TCD-defined VSP was higher in our series compared with the series of Sloan. Sloan demonstrated that TCD VSP occurred in 28% of patients ≥55 and 13% of patients ≥65 years of age. Our higher incidence may be related to a lower CBFV cutoff (≥100 cm/s) compared with the cutoff used by Sloan (120 cm/s).

Our incidence of angiographic VSP was comparable to published data. In 1 study, the reported incidence of angiographic VSP was 75% in patients <60 and 45% in patients ≥60 years of age. Another study reported angiographic VSP in 44% of patients <65 and 23% of patients ≥65 years of age.

The lower incidence of VSP in older patients may be secondary to the age-related increase in atherosclerosis, which results in impairment of contractility and elasticity of the muscle wall of small arteries and arterioles. Postmortem histological studies have demonstrated that aging is accompanied by the appearance of collagen fibers in major intracranial arteries, which is usually associated with loss of elasticity of the vessel wall. Dewey et al described a collapse of downstream vasculature as diastolic pressure falls below the critical closing pressure of cerebral blood vessels. He reported that younger patients, due to more compliant and collapsible vessels, may have greater diminution in CBF as cerebral perfusion pressure reaches a critical closing pressure. Hence, elderly subjects with stiffer vessels may be able to maintain small-vessel patency at similar pressures.

In our series, older patients not only had a low CBFV, but also developed symptomatic VSP at normal-range CBFV. For older patients with SAH (whose resting CBF is lowest), the margin between adequate CBF and the ischemic threshold may become especially narrow. Accordingly, we think that older patients would be susceptible to ischemic neurological deficits induced by small changes in vessel caliber. This discordance between TCD measured CBFV and CBF in older patients with SAH may be due to disturbances in cerebral autoregulation.

The high-risk period to development of symptomatic VSP usually extends from days 4 to 21, with a peak incidence around day 14 after SAH. We found similar risk period in our younger patients, in whom the risk of symptomatic VSP was present until day 16 of SAH. Surprisingly, older patients had a shorter risk period. None of these patients developed symptomatic VSP after day 10 of SAH. We do not have a clear explanation as to the difference in risk-period duration. However, because the diagnosis of symptomatic VSP was not made prospectively, this finding will need to be tested prospectively before therapeutic inferences can be made.

Effect of Age on TCD Sensitivity and Specificity

High specificity and low sensitivity for detecting symptomatic VSP characterize TCD data after SAH in the present study. Specificity and sensitivity in MCA and ICA varied from 85% to 100% and from 25% to 94%, respectively, in the studies of Grolimund et al and Sloan et al. Neither of these studies have taken into account the effect of age on CBFV. Sloan demonstrated that lowering the criterion for diagnosis of TCD VSP from 110 to 80 cm/s improved TCD specificity. In the present study, the high specificity and low sensitivity of TCD in elderly patients may be secondary to lower incidence of VSP and higher false-positive rate in those patients. The false-positive rate in older patients was 40% compared with 27% in younger patients.

Regression Model

Boecher-Schwarz et al was the first to describe a negative linear correlation between the measured MCA MMFV and age (rt = −0.525, P < 0.01) in SAH patients. In this linear model, the authors did not adjust for days of SAH when
CFBV was measured and for presence of symptomatic VSP on that day. To our knowledge, the present study is the first to report an effect of age on CBFV using nonlinear regression analysis and adjusting for factors such as days after SAH and presence or absence of symptomatic VSP.

The slope of the age-related decline in CBFV varied with the vessel insonated and age group of the patients. Why the slopes of the MCA and ICA were not concordant is unclear. In the ICA, most patient MFV decline occurred at a younger age. In the MCA, the major decline in MFV occurred in older patients (≥68 years). This pattern of CBFV changes appears to fit a quadratic model better than a linear model, as our analysis demonstrated. This predictive model could be extrapolated to create an age-adjusted nomogram for CBFV to improve sensitivity and specificit of TCD.

Finally, the present study has a few limitations. Our quadratic model is limited by the retrospective nature of some of the variables included in the analysis. The diagnosis of symptomatic VSP, although it was established through accurate chart review, is retrospective and could overestimate the incidence of VSP in the study. This diagnosis also could affect interpretation of the accuracy parameters of CBFV measured by TCD.

Despite these limitations, we were able to demonstrate in the present study the important nonlinear effect of age on CBFV in patients after SAH. The present study is the first to show that older patients develop symptomatic VSP at normal-range CBFV, which thus limits the application of TCD in the management of elderly SAH patients. An age-adjusted CBFV nomogram in SAH may improve accuracy of TCD in older patients.

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