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Effect of age on transcranial Doppler velocities in patients with aneurysmal subarachnoid hemorrhage

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Abstract

Background—It is not well understood whether age impacts transcranial Doppler (TCD) mean flow velocities (MFV) in patients with aneurysmal subarachnoid hemorrhage (SAH) with or without delayed cerebral ischemia (DCI). The aim of our study was to analyze the behavior of TCD MFV during the first 7 days after SAH in patients of different ages and correlate them with the occurrence of DCI.

Methods—Databank analysis of patients with SAH admitted between 2010–2012 in a single center. We analyzed mean MFV of bilateral middle cerebral arteries in all patients enrolled in the study on days 1, 3 and 7. The correlation between age and TCD MFV was analyzed using a univariate linear regression model.

Results—55 patients were studied. Starting on the 3rd day after the bleeding, increasing age was associated with slower MFV velocities. This trend was not affected by the interrogation of the right or left MCA. After correction to include only patients who developed DCI, the same findings persisted on days 3 and 7.

Conclusion—Older age was correlated with a significant decrease on TCD velocities in patients with SAH, even after correction for patients who developed DCI.

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Keywords

Subarachnoid Hemorrhage; Intracranial vasospasm; Transcranial Doppler Sonography; Age Groups

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Introduction

Delayed cerebral ischemia (DCI) is a serious complication of aneurysmal subarachnoid hemorrhage (SAH). It occurs in around 30% of patients during the initial 14 days after SAH, and it is linked to substantial disability and death¹. Vasospasm is the consequence of intracranial arterial narrowing, resulting from vasoconstriction, swelling of the vascular endothelium, remodeling of the media and/or subendothelial fibrosis^{1,2}. The resulting narrowing can lead to decreased cerebral blood flow, with consequent cerebral ischemia or infarction³. Vasospasm is historically associated with clinical deterioration due to DCI⁴, with consequent cerebral infarction⁵, even though DCI can potentially develop without apparent radiographic correlate^{1,6}. Angiographic vasospasm develops in approximately 70% of patients⁷, and only 20% to 40% of them will ultimately develop neurological deficits or infarction associated with DCI^{5,7,8}. First studied by Aaslid in the early 1980s⁹, transcranial Doppler sonography (TCD) is a non-invasive method to evaluate indirectly the presence of narrowing of intracranial vessels. Studies suggest that mean flow velocities (MFV) of the middle cerebral artery (MCA) lower than 120cm/s correlate with the absence of vasospasm, while velocities higher than 200cm/s suggests a higher probability of vasospasm after aneurysmal SAH^{3,10}.

It is an open question whether age is a risk factor for the development of vasospasm, with conflicting data for both sides of the argument^{11–13}. Prior studies have shown that even among healthy individuals, older age is correlated with slower velocities on TCD^{14,15}. Interestingly, elderly patients can develop DCI while demonstrating slower MFV's than younger patients¹³. The sensitivity of TCD for detection of angiographic vasospasm (aVSP) in the middle cerebral artery (MCA) is broad (ranges from 39% to 85%)^{16–18}. With this broad range, it is difficult to confidently determine the sensitivity in different ages but one study suggested that the sensitivity is lower among elderly patients¹³. The aim of our study was to analyze the behavior of TCD MFV during the first 7 days after SAH in patients of different ages and correlate them with the occurrence of DCI.

Methods

A databank of aneurysmal subarachnoid hemorrhage patients was created using patients admitted between 2010– 2012 in a large quaternary academic center in Cleveland, Ohio, USA. Fifty-five patients admitted through this period with aneurysmal subarachnoid hemorrhage (SAH) were included in our study. The entry criteria consisted of any patients with confirmed aneurysmal subarachnoid hemorrhage on head CT scan and cerebral angiogram, who stayed at least seven days in the hospital (counted from the day of bleeding) and with information available for all the study variables.

We analyzed mean flow velocities (MFV) of bilateral middle cerebral arteries in all patients enrolled in the study on days 1, 3 and 7. We chose to analyze the first seven days after bleeding, as this is the peak period for occurrence of vasospasm in most patients with SAH. It is a matter of debate in the literature whether vasospasm is first observed in the third^{3,19} or the fourth¹ day after bleeding. Age was also collected and used as the concurrent variable. We scanned bilateral middle cerebral arteries using depth references for M2 (arbitrarily located at 30–40 mm depth), M1 (40–65 mm) MCA [with M1 MCA mid-point at 50 mm (range 45–55 mm)], accordingly to the protocols suggested by the American Society of Neuroimaging Practice Guidelines Committee²⁰. Lindegaard indexes were recorded for both sides. All TCD scanning was performed by a team of 3 experienced registered vascular technologists, with every daily sonogram of a patient being performed always by the same technologist.

We defined DCI as clinical deterioration deemed secondary to vasospasm (confirmed with digital subtraction angiography) after other causes were eliminated (such as fever, infection, hyponatremia, seizures, hydrocephalus) and radiographic vasospasm as arterial narrowing diagnosed on digital subtraction angiography^{3,21}. Moderate narrowing was defined as at least 50% decrease in vessel lumen. In comatose patients, DCI was defined as new infarcts on brain computed tomography or magnetic resonance scans, and not deemed to be secondary to endovascular procedures^{3,21}.

Statistical analysis

The correlation between age and TCD MFV was analyzed using a univariate linear regression model. We analyzed the velocities of the right and left MCAs separately, on days 1, 3 and 7. Using linear regression analysis, a p value of the correlation was calculated, coefficients of correlation and regression were derived, as well as the calculated mean velocities for each side daily. Graphic visualization was used to test for residual effects and to identify outliers. A p value of <0.05 was pre-defined as significant. Statistical software IBM SPSS Statistics for Windows®, version 22.0 (Armonk, NY) was used for all analyses.

Results

Fifty-five patients with aneurysmal SAH were analyzed. Characteristics of participant patients are presented in table 1. On day 1 there was no correlation between age and MFV, regardless of which side was insonated. However, starting on day 3 a significant trend became apparent, which was maintained on the 7th day after subarachnoid hemorrhage. In the initial period of vasospasm (3rd day after the bleeding), increasing age is associated with slower MFV velocities. This trend was not affected by the interrogation of the right or left MCA. After correction to include only patients who developed DCI, the same findings persisted on days 3 and 7.

To better refine our study analysis, we conducted a univariate logistic regression analysis to assess whether age was correlated with the occurrence of DCI, but no statistical significance was reached (p<0.89, CI 0.95–1.05). Table 2 shows the p values, mean MFV and regression coefficients for the right and left sides on days 1, 3 and 7. Figure 1 depicts the graphics of

the linear regressions performed on data from days 1, 3 and 7 with all patients included; figure 2 represents only the patients who developed DCI.

Discussion

Our study demonstrated that age has an important effect on TCD MFV, independent of the incidence of DCI. Though it has previously been reported that elderly patients can develop DCI with relatively slower velocities¹³, this is the first study to demonstrate this phenomenon over the period of time from the initial hemorrhage to the period of vasospasm. It is interesting to note that on the first day after bleeding this correlation was not present, suggesting that other factors might influence the MCA MFV later on, such as lower cardiac output, severity of vessel narrowing or different degrees of systemic inflammation, as well as the presence of cerebral edema and consequent intracranial hypertension. The pulsatility index (PI) might be used as a surrogate marker for intracranial hypertension, and higher values might indicate its presence. A post-hoc testing did not find statistical correlation between age and PI on the first day after bleeding. The occurrence of DCI is linked to the presence of systemic inflammation in previous studies^{22–26}, and vasospasm seems to occur more frequently in younger patients^{13,27,28}. A possible explanation would be that younger patients likely mount a more pronounced systemic inflammatory response, not seen during the early period. Other possible explanations would be cardiac deterioration in elderly patients throughout hospital stay, as well as less constriction of their cerebral arteries during the vasospasm period. Aging has been correlated with stiffening of intracranial arteries, as well as decreased cerebral blood flow and vascular compliance^{29–32}. In consequence, elderly patients might experience a slower rise in MFV when compared to younger ones. Finally, when analyzing Lindegaard indexes of all patients, we did not find patients with MFV>120cm/s with an index<3, meaning that probably no systemic hyperdynamic state significantly impacted MCA MFV.

It is also significant that the current predictive thresholds for TCD MFV (<120cm/s and >200cm/s) may not be applicable to elderly patients. It may be reasonable to analyze the trend of TCD MFV changes in this population to better assess the likelihood of incipient vasospasm; daily measurements of MFV may be helpful for this purpose. We hope our study can serve as a hypotheses generator for future larger trials analyzing the sensitivity and specificity of TCD in detecting vasospasm after SAH in different age brackets.

Limitations of our study are the size of our cohort, being a single center study, with MFV analysis confined to the first week after bleeding and restricted to the MCAs.

Conclusion

The current study showed that older age is correlated with a significant decrease on TCD velocities in patients with SAH, and that this finding persists even after correction for patients who developed DCI. It is probably more prudent to use the trend of MFV in elderly patients, instead of relying on a fixed value, to optimize the accuracy of this method when screening for vasospasm in patients with aneurysmal SAH.

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Figure 1.

Linear regression data plotting of TCD mean flow velocities versus age, in patients without DCI, days 1, 3 and 7. LMCA= Left Middle Cerebral Artery; RMCA= Right Middle Cerebral Artery

Figure 2.

Linear regression data plotting of TCD mean flow velocities versus age, in patients with DCI, days 1, 3 and 7. LMCA= Left Middle Cerebral Artery; RMCA= Right Middle Cerebral Artery

Table1

Population characteristics

Variable	Patients with delayed cerebral ischemia	Patients without delayed cerebral ischemia	Statistical difference between groups
Age (median)	55 years	55.5 years	P<0.8941
Gender: Male	2	13	P<0.3596
Female	12	28	
Modified Fisher scale (most prevalent)	4 (40%)	4 (48%)	P<0.5368
Hunt-Hess scale (most prevalent)	3 (42%)	2 (46%)	P<0.6299
Total:	14 (25.45%)	41 (74.55%)	

Table 2

Linear regression data

Linear regressions with all patients included (n=55)			
	<i>Day 1 after SAH</i>	<i>Day 3 after SAH</i>	<i>Day 7 after SAH</i>
Mean of MFV (right/left)	66.72/66.18cm/s	87.83/86.4cm/s	99/89.52cm/s
P value (right/left)	0.0606/0.0526	0.0051/0.0001	0.0035/0.0030
Regression coefficient (right/left)	N/A	-1.05/-1.34	-1.37/-1.01
Linear regressions with only patients who developed delayed cerebral ischemia (n=14)			
	<i>Day 1 after SAH</i>	<i>Day 3 after SAH</i>	<i>Day 7 after SAH</i>
Mean of MFV (right/left)	64.3/65	99.2/94cm/s	108/113cm/s
P value (right/left)	0.6595/0.6725	0.0019/0.0033	0.0422/0.0410
Regression coefficient (right/left)	N/A	-2.60/-2.89	-1.9/-2.4