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Association between transcranial Doppler vasospasm and functional outcome after subarachnoid hemorrhage

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Abstract:

AIM OF THE STUDY: This study aimed to investigate the association between transcranial Doppler (TCD) vasospasm and patient outcome and to assess the predictive factors for developing TCD vasospasm after subarachnoid hemorrhage (SAH).

MATERIALS AND METHODS: This retrospective observational study included adult patients with nontraumatic SAH. Patient characteristics and TCD values were recorded retrospectively from patient records. Data on maxTCD (maximal TCD value recorded on any side between day 1 and day 14) as well as Δ TCD (maximal difference between mean velocity measured on days 1–3 and days 4–14 on any side) were calculated. The modified Rankin Score was recorded from electronic patient notes at discharge and 3, 6, and 12 months after ictus. The effect of TCD vasospasm, maxTCD, and Δ TCD on the clinical outcome was investigated. Potential predictive factors for developing TCD vasospasm were assessed. The association between the same factors and maxTCD and Δ TCD were explored.

RESULTS: One hundred and thirty-eight patients were included in the study. Higher age was associated with a lower risk of developing TCD vasospasm (odds ratio: 0.952, 95% confidence interval: 0.924–0.982, $P = 0.002$). Fisher grade was a predictor of developing TCD vasospasm ($P = 0.05$). Age was negatively correlated with maxTCD ($R = -0.47$, $P = 0.01$). There was no statistically significant difference in patient outcome at hospital discharge and at 3, 6, and 12 months between patients with and without TCD vasospasm. Higher maxTCD and Δ TCD were associated with a worse clinical outcome at 3 months after SAH ictus.

CONCLUSIONS: The clinical benefit of routine TCD assessments in SAH patients remains uncertain.

Keywords:

Cerebral vasospasm, clinical outcome, subarachnoid hemorrhage, transcranial Doppler

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Introduction

Cerebral vasospasm and subsequent ischemia is a feared and potentially devastating complication after aneurysmal subarachnoid hemorrhage (SAH).[1] There are many different definitions of posthemorrhagic vasospasm and related conditions, including symptomatic vasospasm, delayed cerebral ischemia (DCI), angiographic vasospasm, or vasospasm estimated with transcranial Doppler (TCD).[2] Vasospasm is associated with delayed cerebral ischemia and cerebral infarction.[3] Catheter angiography is the gold standard to investigate cerebral vasospasm, but computed tomography angiography (CTA) and TCD are more commonly used due to their less invasive nature.[4] Due to radiation exposure, CTA is usually restricted to confirm clinically suspected vasospasm.[5] Therefore, the

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opportunity to reduce the incidence of vasospasm or detect early and preclinical vasospasm might be lost. TCD, on the other hand, is safe, cheap, noninvasive, and can be used as a daily bedside assessment. A recent systematic review showed that TCD velocity above 120–140 cm/s has a predictive value of 97% for the diagnosis of angiographic vasospasm.[6] Although the use of TCD is recommended by the American Heart Association/American Stroke Association in assessment of patients with SAH, TCD is still not a standard of care in all centers due to its uncertain impact on patient outcomes.[7] Previous studies that investigated the effect of TCD vasospasm on clinical outcome included functional outcome data at discharge only.[7,8] The aim of the present study was to investigate the association between TCD vasospasm and long-term patient outcome and to assess the predictive factors for developing TCD vasospasm after SAH.

Materials and Methods

We performed a retrospective observational study.

Participants

All adult patients with nontraumatic SAH admitted to the Neurointensive Care Unit at St. Olav's University Hospital in Trondheim, Norway, between 2015 and 2020 were eligible for study participation (n = 139). This department is the only neurosurgical unit serving a geographical catchment region with approximately 720,000 inhabitants. Patients who underwent SAH twice in the same year were excluded from the study (n = 1). Patients in whom TCD signal could not be found were excluded from the analysis of TCD data (n = 3).

Outcome data and patient characteristics

Patient characteristics including age, sex, location of the ruptured aneurysm, Hunt and Hess grade, Fisher grade on admission, and treatment received (coiling vs. clipping), as well as TCD values for each patient, were recorded retrospectively from patient records.

It is a common practice in our department to perform TCD on all patients with nontraumatic SAH. TCD is performed by trained medical or nursing staff. TCD is performed through the transtemporal window, and the mean flow velocity in the middle carotid artery (MCA) is obtained bilaterally. Values obtained on the first 3 days after ictus are recorded as a baseline. TCD is then commonly taken multiple times between day 4 and day 14 after ictus, apart from in patients with a very good clinical status who are discharged from the level 2 and 3 Neurointensive Care Unit before day 14. Similar to most other studies, TCD vasospasm was defined as the mean flow velocity over 120 cm/s.[2,6,9]

In addition to TCD vasospasm, data on maxTCD (highest mean TCD value recorded on any side between day 1 to day 14) as well as Δ TCD (maximal difference between mean velocity measured on day 1–3 and day 4–14 on any side) were calculated.

Outcome data were recorded from electronic patient records at discharge from the hospital and at 3, 6, and 12 months after ictus. Clinical outcomes of patients repatriated to their local hospitals after the acute phase and before discharge home or to a rehabilitation center were recorded at discharge from the local hospital. Patients repatriated to hospitals outside the catchment area were excluded from the analysis of outcome data (n = 11). The modified Rankin Score (mRS) was used as a measure of patient clinical outcome. The mRS is a clinician-reported measure of the global disability of patients after stroke. The scale is widely used and validated by multiple studies.[10] A recent literature review provides an extensive description of the scale.[10] The effect of TCD vasospasm, maxTCD, and Δ TCD on the clinical outcome was investigated.

Potential predictive factors for developing TCD vasospasm such as age, sex, location of the ruptured aneurysm, Hunt and Hess grade, and Fisher grade, and treatment received (coiling vs. clipping) were investigated. The association between the same factors and maxTCD and Δ TCD were explored.

Data analysis

Statistical analyses were performed using IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0.1.0 (Armonk, NY: IBM Corp.) (https://www. ibm.com/analytics/spss-statistics-software). The association between patient outcome (mRS) and TCD vasospasm was explored using Mann–Whitney *U*-test. The association between patient outcome (mRS) and maxTCD, and Δ TCD was investigated using logistic regression. The associations were then tested using multivariate logical regression analysis with Fisher grade and Hunt and Hess grade as factors and age as a covariate. Predictive factors for developing TCD vasospasm were analyzed using Chi-square and Kruskal–Wallis tests for categorical and continuous data, respectively. Odds ratios for significant predictive factors were calculated using logistic regression. Logistic regression was also used to perform multivariate analysis. Factors associated with maxTCD were analyzed using Spearman's rank-order correlation for continuous, Kruskal–Wallis test for multicategorical, and Mann–Whitney *U*-test for dichotomous independent variables. Statistical significance was set to $P < 0.05$.

Ethical approval

The Regional Committee for Medical and Health Research Ethics in Central Norway approved the study (2014/958) and waived the requirement of informed consent.

Results

One hundred and thirty-eight patients were included in the study. Table 1 shows the patient characteristics.

Three patients were excluded from the analysis of TCD data because no TCD signal was found. In total, 43 of 135 (32%) patients developed TCD vasospasm. Among these, 15 were investigated with CTA, 13 CTA confirmed vasospasm, and 8 developed DCI. Higher age was associated with a lower risk of developing TCD vasospasm (odds ratio: 0.952, 95% confidence interval: 0.924–0.982, $P = 0.002$), while Fisher grade was a predictor of developing TCD vasospasm ($P = 0.05$) when both univariate and multivariate analyses were performed. Figure 1 shows the distribution of Fisher grade on admission in patients with and without TCD vasospasm.

We found no association between sex, location of the ruptured aneurysm, treatment (coiling vs. clipping), Hunt and Hess grade, and the risk of developing TCD vasospasm. Age was the only factor negatively correlated with maxTCD ($R = -0.47$, $P = 0.01$) [Figure 2].

Table 1: Patient characteristics

Characteristic	Value
Age, mean (SD)	57 (13)
Female, *n* (%)	84 (61)
Location of a ruptured aneurysm, *n* (%)	
ACOM	49 (35.5)
A1	3 (2.2)
Basilar top	8 (5.8)
Carotid	8 (5.8)
MCA	22 (15.9)
PCOM	16 (11.6)
Pericallosal	4 (2.9)
PICA	8 (5.8)
Vertebral	6 (4.3)
No aneurysm found	14 (10.1)
Treatment, *n* (%)	
Clipping	39 (28)
Endovascular intervention	82 (59)
Both	1 (1)
Untreated	16 (12)
Fisher grade, *n* (%)	
Grade 1	0
Grade 2	29 (21)
Grade 3	46 (33)
Grade 4	62 (45)
Hunt and Hess grade on admission, *n* (%)	
Grade 1	40 (29)
Grade 2	21 (15)
Grade 3	37 (27)
Grade 4	22 (16)
Grade 5	18 (13)

SD: Standard deviation, MCA: Middle cerebral artery, ACOM: Anterior communicating artery, PCOM: Posterior communicating artery, PICA: Posterior inferior cerebellar artery

Figure 3 shows the patient clinical outcome (mRS) at hospital discharge and 3, 6, and 12 months after ictus in SAH patients with TCD vasospasm and no TCD vasospasm. There was no statistically significant difference in patient outcome between patients with TCD vasospasm and no TCD vasospasm at hospital discharge ($n = 124$) and at 3 months ($n = 115$), 6 months ($n = 98$), and 12 months after ictus ($n = 85$). No statistical difference between the groups was found at any of the timepoints when the mRS scale was dichotomized into good (mRS ≤ 2) and bad outcome (mRS >2).

Univariate data analysis showed that higher maxTCD and Δ TCD were associated with a worse clinical outcome at 3 months after SAH ictus. These associations were also true when the data were controlled for Fisher grade, Hunt and Hess grade, and age. No significant association between maxTCD and Δ TCD and clinical outcome was found at hospital discharge and at 6 or 12 months after ictus when univariate and multivariate analyses were performed.

Discussion

In this retrospective observational study, we found that age and Fisher grade on admission were predictive factors for developing TCD vasospasm after SAH. MaxTCD velocity was negatively correlated with patient age. As TCD velocity is affected by age,[11-13] one might argue that the Δ TCD might be a better marker of vasospasm in an individual patient. To our knowledge, the association between Δ TCD and vasospasm or patient clinical outcome after SAH has not been previously investigated. In our study, higher maxTCD velocity and Δ TCD were associated with worse clinical outcomes at 3 months after SAH ictus. However, neither maxTCD velocity nor Δ TCD was independently associated with patient outcome at hospital discharge or at 6 and 12 months after SAH. TCD vasospasm was not associated with patient outcome at any of the timepoints.

While it is known that vasospasm is associated with cerebral ischemia and delayed ischemic neurological deficit (DIND) and that TCD may be used to investigate vasospasm, one might argue that the lack of association

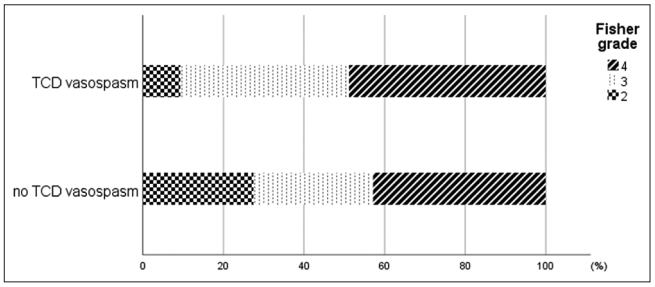

Figure 1: The distribution of Fisher grade on admission in subarachnoid hemorrhage patients with and without transcranial Doppler vasospasm

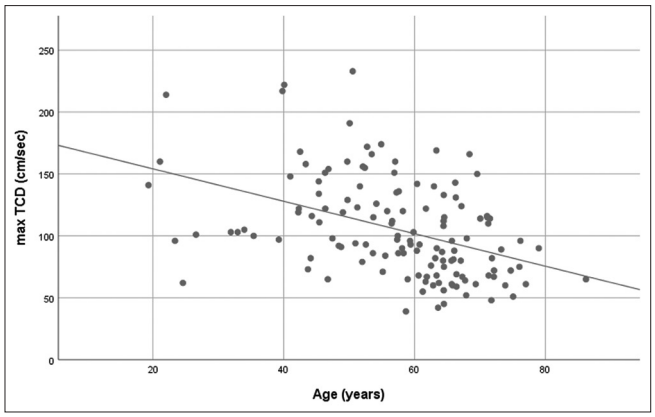

Figure 2: The correlation between max transcranial Doppler and age

with clinical outcome may weaken the potential clinical importance of routine TCD assessments in SAH patients. The obtained results showing no association between TCD vasospasm and clinical outcome might have been confounded by the intensified treatment when vasospasm was diagnosed, and although this study population was reasonably large, power might have been an issue with relatively few patients with definitive DIND. Even so, our findings are in line with a recent prospective study. The authors of the study compared clinical outcomes of SAH patients during two periods with and without TCD assessment. In the cohort assessed with TCD, 24% of patients had TCD vasospasm, defined as mean blood flow over 120 cm/s. The authors found no difference in inpatient clinical outcomes (GOS, mRS, and NIHSS) between groups.[7] Another study investigated the benefit of TCD assessment on clinical outcomes of patients with SAH using data from the United Kingdom and Ireland SAH Registry. The study compared patient outcomes between five neurosurgical departments where TCD is routinely used and seven centers where TCD is not used. The authors found that centers that screened for vasospasm using TCD had poorer inhospital outcomes and similar rates of DCI diagnosis compared to centers that did not use TCD. The study had many limitations including large variability in the TCD screening paradigm across centers. Four of five "screening centers" performed TCDs only on specific patient groups, such as patients with hydrocephalus or large blood load (1 center) or those in level 3 care only (3 centers). In addition, the TCD findings in "screening centers" were not recorded in the registry, and no "screening center" reported the use of a specific treatment algorithm for patients with TCD vasospasm. As a result, the definition of TCD vasospasm could have differed between the centers, and treatments administered to patients with TCD vasospasm are unknown.[8]

Despite the fact that TCD is recommended by the American Heart Association/American Stroke

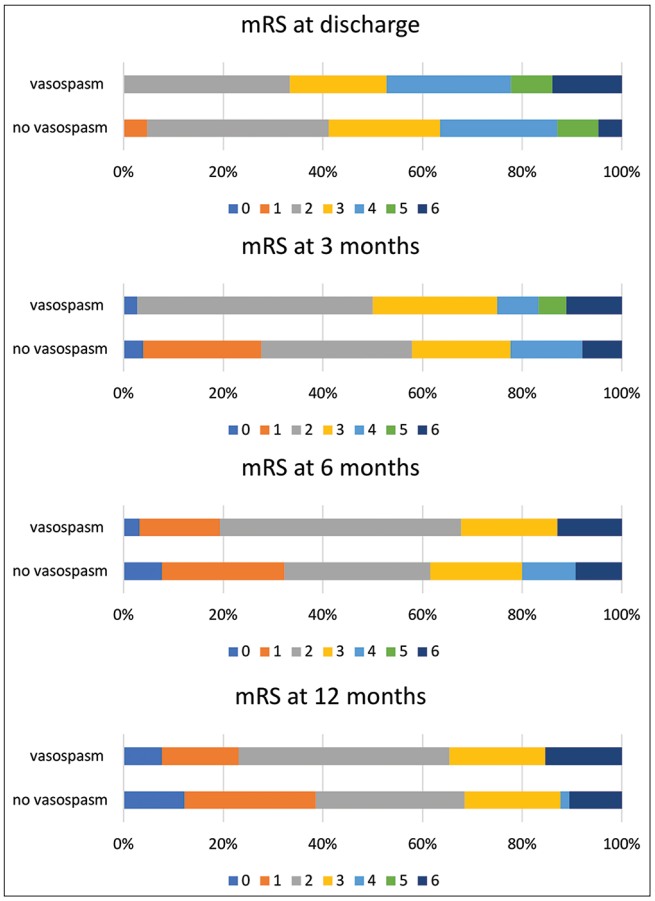

Figure 3: Patient clinical outcome (modified Rankin Score) at hospital discharge and 3, 6, and 12 months after ictus in subarachnoid hemorrhage patients with transcranial Doppler vasospasm and no transcranial Doppler vasospasm modified Rankin Score

Association in assessment of patients with SAH, one may perhaps question if TCD should be defined as standard care based on the limited clinical evidence. It is not known whether "clinical vasospasm," i.e., vasospasm based on clinical symptoms alone, may be a better or just as good alternative. This may enable assessment 24/7 and not only when TCD is performed. Further, the results of TCD are operator dependent, which affects reliability. Moreover, TCD assessment is usually performed on one vessel only, most often the MCA. The obtained value might not be representative of the state of the whole cerebral circulation as it is possible that vasospasm is segmental or local.[14] Moreover, other mechanisms such as microcirculatory dysfunction with loss of autoregulation, microthrombosis, cortical spreading depression, and delayed cellular apoptosis may contribute to DIND.[15,16] Increased intracranial pressure (ICP) at ictus and global hypoperfusion may also, in theory, lead to glial activation, endothelial dysfunction, diffuse neuroinflammation, and subsequent ischemia.[17] Last but not least, treatment of vasospasm is still challenging.[18] Therefore, the potential opportunity to reduce the incidence of clinical

vasospasm by regular TCD screening and treatment might be limited. Treatment with nimodipine and regular monitoring and optimization of electrolytes as well as blood pressure and ICP to target normal levels is commonly performed regardless of the diagnosis of vasospasm. In our department, patients with TCD vasospasm are treated with "aggressive" CSF drainage with an external ventricular drain or lumbar drain, and maintaining adequate cerebral perfusion pressure (usually above 70 mmHg) with the use of intravenous fluids and inotropes if required. Conventional angiography is not used to confirm the vasospasm, but as reported, vasospasm is confirmed with CTA in some patients. Endovascular procedures such as intra-arterial calcium channel blockers or angioplasty are not performed.

Our study is the first to report the effect of TCD vasospasm on clinical outcome during up to 12 months of follow-up. We also present additional TCD data, i.e., maxTCD and Δ TCD, that have not been previously investigated. Another strength of the study is the population-based selection of patients. Nevertheless, due to the study's retrospective design, results can be affected by the missing follow-up data. At hospital discharge, outcome data of 11 patients were excluded due to missing data as a result of repatriation to hospitals outside the catchment area. This is unlikely to introduce selection bias in the study because these patients were excluded at random. The weakness of missing data might be the most significant for the long-term follow-up data (6 and 12 months after ictus). It is likely that patients with good clinical outcomes at 6 and 12 months after ictus are underrepresented in our population as they most likely had less need to seek hospital care months after SAH, therefore, had no patient records available. In addition, the mRS grades were recorded retrospectively from the clinical electronic records which, one could suggest, might have affected the accuracy of the outcome data. We believe, however, that the accuracy was high due to the fact that in most patients, the clinical electronic records included notes from rehabilitation centers and stroke follow-up clinics where clinicians routinely record patient functional levels. In patients where clinical notes were not clear about the functional level of the patients, the data were marked as "missing."

Conclusions

Although there is a correlation between TCD values in SAH patients and age and Fisher grade, we found no clear link to the clinical outcome. The clinical benefit of routine TCD assessments in SAH patients remains uncertain.

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Conflicts of interest

There are no conflicts of interest.

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