Transcranial Doppler velocimetry in aneurysmal subarachnoid haemorrhage: intra- and interobserver agreement and relation to angiographic vasospasm and mortality

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Editor’s key points

- Cerebral vasospasm is a common complication of subarachnoid haemorrhage, resulting in cerebral ischaemia and secondary neurological injury.
- Transcranial colour duplex ultrasonography is a safe, non-invasive method of measuring cerebral blood flow velocity (CBFV).
- A high mean CBFV in the middle cerebral artery (MCA) usually indicates cerebral vasospasm.
- The authors studied inter- and intra-observer variability in MCA flow velocities measured in patients and healthy controls.

Background. Transcranial Doppler measurements of the middle cerebral artery flow velocity are widely used as an indicator of vasospasm after aneurysmal subarachnoid haemorrhage (SAH). We investigated inter- and intraoperator agreement in SAH patients and healthy volunteers using colour-coded transcranial Doppler (TCCD), with the secondary aim of describing prediction of angiographic vasospasm and mortality.

Methods. Sixty patients and 70 healthy controls were each examined in duplicate by alternating operators. A total of 939 measurements divided on 201 examination sets were conducted by four observers. The Bland–Altman limits of agreement (LoA) were calculated using a variance components analysis. Angiography was performed on clinical indication and survival recorded at 30 days.

Results. Differences between measurements increased with increasing average, and therefore, we analysed log-transformed values. Thus, LoA are given as ratios between measurements. There were no systematic intra- or interobserver differences (bias). The intraobserver LoA was 0.62–1.61 in patients and 0.67–1.50 in controls. However, they were 0.55–1.82 in patients with angiographic vasospasm, whereas in patients without, they were 0.66–1.52. The interobserver LoA was 0.55–1.81 in patients and 0.65–1.55 in controls, while in patients with and without angiographic vasospasm, they were 0.45–2.22 and 0.60–1.67, respectively. Flow velocity measurements day 6–10 were positively associated with 30 day mortality risk (P = 0.02, logistic regression).

Conclusions. TCCD measurement variability is wider in patient measurements than in controls. This discrepancy can largely be explained by a higher degree of error in patients with angiographic vasospasm. Despite the considerable measurement variability in TCCD, values are predictive of outcome in SAH.

Keywords: angiography; interobserver variation; outcome; subarachnoid haemorrhage; transcranial Doppler; vasospasm

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Cerebral vasospasm is the most important cause of secondary cerebral ischaemic damage and hence of delayed neurological deficits and poor outcome after aneurysmal subarachnoid haemorrhage (SAH). Diagnosis of this complication is therefore essential in an effective therapeutic strategy. The condition was first described with arteriography which remains a ‘golden standard’ in the diagnosis, although it is limited in availability and is not without risk of complications. Transcranial colour duplex ultrasound (TCCD) is a bedside diagnostic tool widely used in the monitoring of SAH patients. The advantages of TCCD are low cost, easy availability, virtually no complications, and the possibility of conducting daily examinations. A high mean flow velocity in the middle cerebral artery (MCA) is generally interpreted as cerebral vasospasm, although a number of physiological conditions can lead to increased flow velocities. Even though conventional transcranial Doppler (TCD) flow velocimetry was introduced almost 30 yr ago, only a few studies have investigated inter- and intraobserver variation. Furthermore, the field of method validation

1 These authors contributed equally to conception and design of the experiments, collection, analysis and interpretation of data, and drafting the article.
suffers from the frequent use of non-transparent statistics such as correlation coefficients and the coefficient of variance, which may limit interpretation and hence translation to clinical application.\textsuperscript{8–10,12} Other studies regarding TCD/TCCD methodology focus either on the ability to predict angiographic vasospasm or secondary neurological ischaemic deficits.\textsuperscript{13–15} A recent meta-analysis concludes that dichotomized TCD values have high positive, but poor negative, predictive value compared with angiography, although the authors also conclude that the underlying quality of the data is variable.\textsuperscript{16} Few studies concern conventional TCD vs TCCD,\textsuperscript{17,18} which are often treated as interchangeable modalities, although this is not necessarily justified. TCD/TCCD is currently recommended as part of the monitoring of SAH patients,\textsuperscript{19} but interpretable inter- and intraoperator characteristics of TCCD as applied in the critical care setting of SAH patients is necessary for a rational clinical use of the method.

The primary aim of the present work was to prospectively analyse agreement in TCCD measurements in the clinical monitoring of SAH patients and compare with a healthy control group. We also investigated TCCD agreement in patients with and without angiographically proven vasospasm. We used the limits of agreement (LoA) method proposed by Bland and Altman\textsuperscript{12} as it provides a clinically interpretable estimate of measurement error. Secondly, to enable comparison with previous studies regarding diagnostic performance, we investigated the accuracy (sensitivity and specificity) and likelihood ratios of MCA flow velocity measurement to radiologically assessed cerebral vasospasm and compared both of these modalities with survival.

**Methods**

**Subjects**

Patients with aneurysmal SAH admitted to the Neurointensive care unit at the Copenhagen University Hospital (Rigshospitalet) were included. The diagnostic criterion was spontaneous SAH caused by the rupture of an intracranial saccular aneurysm. Sixty-seven patients with spontaneous SAH were initially included; however, seven were later excluded because no saccular aneurysm was verified. Five patients turned out to have inadequate cranial windows leaving 55 patients contributing to data analysis. Patients or close relatives provided information on a pre-designed questionnaire regarding smoking, alcohol habits, medication, arterial hypertension, diabetes, and familial disposition. The total study period was 1 yr and 9 months. Seventy healthy volunteers were recruited among personnel at the Department of Neuroanaesthesiology at the Copenhagen University Hospital (Rigshospitalet), provided they had no history of intracranial disease. Smoking or treatment of arterial hypertension was not considered causes for exclusion. The group of healthy volunteers was included over the same time period as the patients. All patients were treated with prophylactic nimodipine (60 mg × 6/day, 21 days). Cases of cerebral vasospasm were treated with induced hypertension and hypervolaemia.

**Ethics**

Written informed consent was obtained from all participants or next of kin. The study was approved by the Regional Ethics Committee of Copenhagen (H-A-2008-033).

**Study design**

Four observers took part in the study. All of them were experienced TCCD users. Patients had one to six sets of measurements taken in a period of up to 15 days after aneurysm rupture. A maximum of one measurement set was taken per day. Healthy volunteers were examined on one occasion. All subjects were examined in the supine position after at least 10 min of rest.

Insonation of the MCA M1 segment was performed bilaterally through the transtemporal acoustic window using colour-coded duplex ultrasound (Micromaxx, Sonosite Ltd, Hitchin, UK; P17/5 1 MHz probe). Briefly, the butterfly-shaped mesencephalic brainstem was seen as an anatomical B-mode landmark before colour-coded identification of the posterior and middle cerebral arteries. An optimal signal was sought out (according to internal guidelines preferably in a depth of 4.5–5.5 cm), the screen was frozen, and the mean flow velocity during one cardiac cycle recorded by the main investigator (T.E.).

A set of measurements were obtained by two observers (A and B) with the following four steps. First, observer A would measure the mean flow velocity in the MCA bilaterally. Secondly, observer B would measure the mean flow velocity in the MCA bilaterally blinded to the results of observer A. Thirdly, observer A repeated his examination blinded to the results of observer B. Fourthly, observer B repeated his examination.

Angiography (digital subtraction angiography or CT angiography) was performed at the discretion of the treating neurosurgeon, when clinical signs of cerebral vasospasm were present (decrease in GCS, development of focal neurological deficits, and/or sudden arterial pressure increases) and other aetiologies seemed unlikely. The radiologist’s dichotomized assessment (yes/no) of vessel calibre reduction compared with contralateral vessels or ipsilateral in earlier angiograms was obtained for analysis. Thus, angiographical vasospasm was defined as a positive angiogram preceded by relevant symptoms.

**Statistical analysis**

Statistical analysis was done using the open source statistical software ‘R’ version 2.14.1 Mac GUI with the additional package ‘lme4’.\textsuperscript{20,21} Intra- and interobserver variation were characterized using the LoA method described by Bland and Altman.\textsuperscript{22} We conducted a variance component analysis in a linear mixed effects model using the ‘lme4’ package, to take into account the unbalanced study design with multiple bilateral
measurements per subject and several measurement days and observers. The mixed model we used can be generally formulated as:

\[ Y_{ij} = \mu + \xi_j + \epsilon_{ij} \]  

(1)

where \( Y_{ij} \) is the \( i \)th measurement of the mean flow velocity of the \( j \)th subject, \( \mu \) the population mean (fixed effect), \( \xi_j \) the subject-specific level of the response (random effect) and \( \epsilon_{ij} \) the measurement error of the \( i \)th measurement of the \( j \)th subject. We extended this model to include fixed effects of day (\( \mu_d \)), positive angiography (\( \mu_2 \)), dichotomized WFNS-grade (\( \mu_3 \)), good: I, II, bad: III, IV, V, \( \xi \) subject age (\( \mu_4 \)), observer (\( \mu_5 \)), observer order (\( \mu_6 \)), order of observers measurements (\( \mu_7 \)), and side (\( \mu_8 \)). We included random effects of subject (\( \xi \)) and interactions with patient and side (\( \xi_{p,s} \)), observer (\( \xi_{p,o} \)), day (\( \xi_{p,d} \)), side and observer (\( \xi_{p,s,x,o} \)), and side and day (\( \xi_{p,s,x,d} \)). Random effects of the observer within patient, side, and day (\( \xi_{p,s,x,d,o} \)) and observer within patient and day (\( \xi_{p,s,x,d,o} \)) were removed in a stepwise manner as they had zero variance. Model parameters were estimated using the restricted maximum likelihood criterion. The full model used can be formulated:

\[ Y_{p,s,d,o} = \mu_{o,a} + \xi_{p} + \xi_{p,s} + \xi_{p,o} + \xi_{p,d} + \xi_{p,s,x,o} + \xi_{p,s,x,d} + \epsilon \]  

(2)

The total variance of this model is the sum of the variances of the random effects:

\[ \sigma^2_{total} = \sigma^2_{\xi} + \sigma^2_{\xi_{p,s}} + \sigma^2_{\xi_{p,o}} + \sigma^2_{\xi_{p,d}} + \sigma^2_{\xi_{p,s,x,o}} + \sigma^2_{\xi_{p,s,x,d}} + \sigma^2_{\epsilon} \]  

(3)

The analysis was performed in the full patient population, in the subset of patients with and without angiographic vasospasm (\( \mu_2 \) removed) and in healthy controls (\( \mu_1 \), \( \xi_{p,o} \), and \( \xi_{p,s,d} \) removed).

The variance between observers in the same subject at the same time was termed the interobserver variation. Variance within observers on the same subject at the same time was denoted intraobserver variation. Inter- and intraobserver bias was defined as the model’s fixed effects of investigator order (\( \mu_4 \)) and observation order (\( \mu_5 \)), respectively. LoA was calculated as bias [2\( \sqrt{\text{sum of the respective variance components}} \)]. We constructed the Bland–Altman plots of the differences against the average of paired measurements and added the LoA and bias as horizontal lines. As the scatter of paired differences increased with the average flow velocity values, the log-transformed flow velocities were analysed instead of absolute values. This led to an equal scatter of paired differences and normal distribution of model residuals. Back-transforming the bias and LoA from the log-scale to ratios allow us to discuss relative bias and proportional agreement as suggested by Bland and Altman.\(^{12}\)

We also explored the effect of averaging each investigator’s observations on the interobserver variation and calculated LoA with the same variance decomposition as described above.

The predictive ability of TCCD vs angiographic vasospasm and 30 day survival was tested in two logistic regression models. The sensitivity and specificity of cut-off values were calculated in the range of 80–250 cm \( \text{s}^{-1} \) and used to construct a receiver operating characteristics (ROC) curve (sensitivity vs 1-specificity); area under the curve was calculated with the Mann–Whitney approach.\(^{24}\) In these models, we analysed by-subject summary measures of TCCD measurements to avoid repeated measurements correlation problems. The TCCD summary measure related to angiographic vasospasm was calculated by averaging the subset of

<table>
<thead>
<tr>
<th>Table 1 Patient summary statistics (n=60)</th>
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<tbody>
<tr>
<td>Women [n (%)]</td>
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<tr>
<td>Age [mean (range)]</td>
</tr>
<tr>
<td>BMI [mean (o)]</td>
</tr>
<tr>
<td>Smokers [n (%)]</td>
</tr>
<tr>
<td>Anti-hypertensive medication [n (%)]</td>
</tr>
<tr>
<td>Treatment: coiling/surgical clipping/none [n (%)]</td>
</tr>
<tr>
<td>Angiographic vasospasm [n (%)]</td>
</tr>
<tr>
<td>Timing of positive angiography [median day (1st–3rd quartile)]</td>
</tr>
<tr>
<td>Fisher grade: I/II/III/IV [n (%)]</td>
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<tr>
<td>30 day survival [n (%)]</td>
</tr>
</tbody>
</table>

The ROC curve of TCCD and angiographic vasospasm used the area under the curve (AUC) to assess the discrimination of the TCCD measurements in controls and patients in relation to angiographic vasospasm. Population means of mean flow velocity recordings. Error bar: ± 2 SD. WFNS, World Federation of Neurosurgical Societies SAH grading scale.\(^{23}\)

measurements taken in angiography positive subjects on the
day of positive angiography and 3 days prior. Likewise, the
TCCD measurements taken on days of negative angiography
± 2 days were averaged and associated with negative angiographic vasospasm (if several negative angiographies were
performed all measurements in the respective interval were
used). In the case of conflicts between these two criteria,
the TCCD measurement was associated with positive angiography (n=1). With regard to 30 day survival, we averaged all
TCCD measurements taken day 6–10 in a given patient. As-
sociation between angiographic vasospasm and 30 day sur-
vival was tested with Fisher’s exact test of a 2×2 contingency table.

**Results**

Sixty patients and 70 healthy volunteers participated in the
study. Patient characteristic data are presented in Table 1.

The control group consisted of 47 (67%) women with the
mean age of 44 (range 23–63) yr. The statistical analysis is
based on a total of 939 TCCD successful measurements
divided on 201 examination sets conducted by the four
observers. TCCD measurements of MCA flow velocity in the
study period are shown in Figure 1, where a trend towards
increased flow velocities day 6–10 and in patients with
poor clinical grade and/or angiographic vasospasm at any
time during study period is observed. The average flow
velocity during day 6–10 was 18% (confidence interval:
8–30%) higher than the average flow velocity day 0–5
(paired t-test, P=0.001, t=3.86, df=18).

**Intra- and interobserver variation**

Scatter plots and the Bland–Altman plots of the original intra-
and interobserver paired measurements in the
patient and control groups are shown in Figure 2. The

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**Fig 2 Intra- and interobserver measurements.** (A) Intraobserver analysis: scatterplot of observer’s first and second measurements. (A) Interobserver analysis: scatterplot of first observer’s vs second observer’s measurement. (C) Intraobserver analysis: the Bland–Altman plot of paired differences vs averages of points in (A). (D) Interobserver analysis: the Bland–Altman plot of paired differences vs averages of points in (A). Solid line denotes the line of equality.
Bland–Altman plots of log-transformed intra- and interobserver paired measurements with LoA and bias are shown in Figure 3. The log-transformation which was used as measurement error was observed to increase with increasing patient measurements (Fig. 2). This relation was not as evident in controls, probably because the measurements were relatively closer and of less magnitude. However, values in both groups were log-transformed to enable comparison (Fig. 3). Intra- and interobserver LoA were calculated based on the variance components (Table 2) of the mixed effects model (equation 2). Bias was left out of these calculations as it was negligible for both order of measurements and order of investigators. LoA is expressed as a ratio between two observations and presented in Table 3. Notably, LoA in patients without angiographic vasospasm is similar to that of healthy controls. When averaging each observer’s measurements, a reduction in the LoA was observed (last column, Table 3).

Prediction of angiographic vasospasm and mortality
TCCD by-subject summary measures were significantly associated with both 30 day mortality ($P=0.016$, Wald’s $\chi^2$) and angiographic vasospasm ($P=0.001$, Wald’s $\chi^2$) in univariate logistic regression models. The corresponding model predicted probabilities and likelihood ratios of angiographic vasospasm and 30 day mortality are shown in Figure 4. Flow velocity summary measures in the range from 150 to 200 cm s$^{-1}$ do not improve the likelihood of angiographic vasospasm, but values outside this range increases certainty, although the confidence interval is wide (Fig. 4). Similarly, summary measures below 150 cm s$^{-1}$ are associated with good survival prognosis, whereas values above 250 cm s$^{-1}$ dramatically increase mortality risk. Inclusion of sex and age as covariates in the logistic regression models did not improve fit. The ROC curve (Fig. 5) illustrates that no ideal single threshold exists. The area under the curve was 0.80, which can be considered moderate performance.

![Fig 3](https://example.com/fig3.png)

**Fig 3** Proportional bias and LoA in TCCD measurements in patients and volunteers. The Bland–Altman plots of ratios between pairwise measurements against averaged pairwise measurements. Proportional bias and LoA as calculated with variance component analysis are depicted as horizontal lines. (A) Intraobserver agreement in controls. (B) Intraobserver agreement in patients. (C) Interobserver agreement in controls. (D) Interobserver agreement in patients.
Furthermore, there was no association between angiographic vasospasm and 30 day mortality ($P=0.69$, Fisher’s exact test); however, the 95% confidence interval of the associated odds ratio is very wide (0.2–8.5).

**Discussion**

For the first time, we report intra- and interobserver LoA of agreement in TCCD measurements of the MCA mean blood flow velocity in patients with SAH and compare them with a healthy control group. We find that they are wider in SAH patients: two measurements taken within ~15 min, on the same vessel, in the same patient, by the same observer, might well be within a ratio of 0.62–1.61 of each other. This is in good agreement with the findings by Venkatesh and colleagues,25 who reported a moment-to-moment variability of −38% to 78% in patients and −31% to 58% in volunteers. For measurements made by different observers, LoA is wider (Table 3). However, the variance component analysis (Table 2) shows that whereas the intraobserver variance (residual variance) accounts for 27% of the total variance in patients and 33% in volunteers, the interobserver variance accounts for 15% in patients and only 5% in volunteers. This indicates that the greater part of the measurement variability does not stem from interobserver variation.

When stratifying the patient population according to angiographically verified vasospasm, the wider measurement error in patients compared with controls seems to be due to an extremely large measurement error in patients with angiographic vasospasm in contrast to the group without, which is almost identical to the control group. McMahon and colleagues26 found LoA up to ±40 cm s$^{-1}$ in healthy subjects when comparing experienced and inexperienced observers, which is in agreement with the results of our control group (e.g. a mean flow velocity of 80 cm s$^{-1} \times 155\% = 124$ cm s$^{-1}$, which is equal to an upper limit of agreement of ±44 cm s$^{-1}$). Flow velocities within our control group (Fig. 1) may appear higher than usually reported with conventional TCD, but are in line with reference values previously reported for TCCD.26

Our results indicate that biological factors associated with angiographic vasospasm influence measurement error. In part, this could stem from a higher degree of moment-to-moment variation, which has been shown to occur in a small ($n=8$) sample of patients with continuous TCD.25 This may be due to medical interventions like calcium antagonists and triple-H therapy, which is likely to be more aggressively administrated in patients with angiographic vasospasm. Furthermore, vessel narrowing acting together with haemodilution and hypertension will increase the tendency to turbulent

**Table 2** Variance components. *Random effect terms in mixed model (equation 3). †Variance components in four models of the log-transformed flow velocities with different subsets of the population. The first seven rows in each column sum to the total model variance (8th row). All values in the table are times $10^{-2}$

<table>
<thead>
<tr>
<th>Variance components*</th>
<th>Symbol</th>
<th>All patients$^{\dagger}$</th>
<th>Patients with angiographic vasospasm$^{\dagger}$</th>
<th>Patients without angiographic vasospasm$^{\dagger}$</th>
<th>Healthy controls$^{\dagger}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residual variance</td>
<td>$\sigma^2$</td>
<td>2.80</td>
<td>4.51</td>
<td>2.19</td>
<td>2.05</td>
</tr>
<tr>
<td>Subject</td>
<td>$\sigma^2_P$</td>
<td>2.31</td>
<td>0.00</td>
<td>3.07</td>
<td>3.62</td>
</tr>
<tr>
<td>Subject x side</td>
<td>$\sigma^2_{P \times S}$</td>
<td>1.29</td>
<td>0.59</td>
<td>1.54</td>
<td>0.32</td>
</tr>
<tr>
<td>Subject x observer</td>
<td>$\sigma^2_{P \times O}$</td>
<td>0.32</td>
<td>1.86</td>
<td>0.00</td>
<td>0.31</td>
</tr>
<tr>
<td>Subject x day</td>
<td>$\sigma^2_{P \times D}$</td>
<td>1.35</td>
<td>0.42</td>
<td>2.09</td>
<td>—</td>
</tr>
<tr>
<td>Subject x side x observer</td>
<td>$\sigma^2_{P \times S \times O}$</td>
<td>1.30</td>
<td>1.60</td>
<td>1.06</td>
<td>0.01</td>
</tr>
<tr>
<td>Subject x side x day</td>
<td>$\sigma^2_{P \times S \times D}$</td>
<td>1.09</td>
<td>1.77</td>
<td>0.86</td>
<td>—</td>
</tr>
<tr>
<td>Total model variance</td>
<td>$\sigma^2$</td>
<td>10.45</td>
<td>10.74</td>
<td>10.82</td>
<td>6.30</td>
</tr>
</tbody>
</table>

**Table 3** LoA in ratios between observations. *Subset of data entered in mixed effects model. †LoA within subject, side, day and observer calculated as $e^{\pm \sqrt{2} s^1}$. $s^2$ can be found in Table 2. Bias was negligible and was not entered in the above calculations. ‡LoA within subject, side, day between observers calculated as $e^{\pm \sqrt{2} s^1}$, $s^2$ can be found in Table 2. ‡LoA within subject, side, day between observers calculated as $e^{\pm \sqrt{2} s^1}$, variance components can be found in Table 2. †LoA within subject, side, day and observer calculated as $e^{\pm \sqrt{2} s^1}$, variance components can be found in Table 2.

<table>
<thead>
<tr>
<th>Group*</th>
<th>Intraobserver limits of agreement$^{\ddagger}$</th>
<th>Interobserver limits of agreement$^{\ddagger}$</th>
<th>Interobserver limits of agreement, averaged measurements$^{\ddagger}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>1.61–0.62</td>
<td>1.81–0.55</td>
<td>1.50–0.67</td>
</tr>
<tr>
<td>Patients with angiographic vasospasm</td>
<td>1.82–0.55</td>
<td>2.22–0.45</td>
<td>1.68–0.59</td>
</tr>
<tr>
<td>Patients without angiographic vasospasm</td>
<td>1.52–0.66</td>
<td>1.67–0.60</td>
<td>1.45–0.69</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>1.50–0.67</td>
<td>1.55–0.65</td>
<td>1.45–0.69</td>
</tr>
</tbody>
</table>
flow. Also, impaired cerebral autoregulation associated with angiographic vasospasm could contribute to an increased variability in cerebral blood flow velocity. A practical approach to overcome measurement error problems is to average several measurements, thus taking advantage of the ‘regression towards the mean’ phenomenon. We showed that duplicate measurements can narrow the LoA to some extent (Table 3). However, if this approach is used without regard to the original recorded values, the clinician will of course lose information about variability, which might be clinically important. As an analogy, heart rate variability in head trauma patients and blood glucose variability in euglycaemic critically ill patients are both predictive of mortality.

The clinical relevance of conducting TCCD measurements in SAH patients has been questioned. Our results indicate that if used as an indicator of angiographic vasospasm, the diagnostic decision process will not be aided if values are within the range of 140–200 cm s$^{-1}$, while values outside this range increase the likelihood to either side dramatically (Fig. 4). Thus, TCCD values above 200 cm s$^{-1}$ should increase clinical suspicion of vasospasm, while values below 140 cm s$^{-1}$ should lower it. The ROC curve (Fig. 5) with an area under the curve of 0.80 emphasizes the fact that no

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**Fig 4** TCCD prediction of angiographic vasospasm and 30 day mortality. (a) Probability of angiographic vasospasm depending on average TCCD values in the time frame of angiography as predicted by logistic regression model (see the Methods section for details); dotted line is equal to 100% minus the bold line. (a) Diagnostic likelihood ratios (or odds) derived from the model probabilities in (a); dotted line is equal to the inverse of the bold line. (c) Probability of 30 day mortality depending on the average TCCD values day 6–10 as predicted by logistic regression model (see the Methods section for details); dotted line is equal to 100% minus the bold line. (b) Diagnostic likelihood ratios (or odds) derived from the model probabilities in (c); dotted line is equal to the inverse of the bold line. Shaded area signifies 95% confidence interval of fit in all panels.
single threshold is ideal. In line with this, Mariak and colleagues reported ROC curves with an area under the curve of 0.80 for MCA flow velocity measurement vs any degree of angiographic vasospasm. This result should, however, be interpreted with caution as the decision to perform angiography was not always independent of flow velocity measurements.

The 30 day mortality rate of our patient sample was 15%, which is lower than the general SAH mortality. This may be due to selection bias because patients dying in the early hours after aneurysm rupture were not as likely to be considered for inclusion. Interestingly, we found a significant positive association \( (P=0.016) \) between average flow velocity day 6–10 and 30 day mortality, whereas none was found between angiographic vasospasm and 30 day mortality. This has not been reported previously and we therefore regard it as a hypothesis generating finding. One explanation between the apparent discrepancy between angiographic and velocimetric associations with mortality is that high MCA flow velocities associates with other conditions than vessel narrowing, for example, anaesthetics, infection, \( P_{\text{CO}_2} \) increase, i.e. fluid therapy, which may all be confounders of mortality. Also, previous TCD studies mostly analysed flow velocity recordings as a categorical variable (e.g. above or below certain limits such as 200 cm s\(^{-1}\)), which limits the statistical power to find such an association.

Despite the considerable measurement variability, our study is not contradicting previous reports on accuracy and the current data support the notion that low flow velocities are indicative of the absence of angiographic vasospasm. The majority of historical data are based on conventional TCD measurements and only a few comparison studies with colour-coded TCD are available. These studies report only correlation coefficients and population means, but do conclude that there is bias towards higher measurements in colour-coded TCD. Whether LoA was the same within and between TCD methods in these studies would require re-analysis of the data.

In conclusion, we report LoA within and between observers in TCCD measurements of time-averaged MCA flow velocity in SAH patients and healthy controls. The LoA is wider in patients than in controls, but this difference can largely be explained by a much more extreme measurement error in patients with angiographic vasospasm. In addition, an association between 30 day mortality risk and high flow velocities day 6–10 after SAH was observed. Altogether, TCCD is associated with considerable inter- and intraobserver measurement variability, which must be taken into account when evaluating the individual patient. Nevertheless, in agreement with previous studies, TCCD flow velocimetry was of predictive value with regard to angiographic vasospasm and outcome, when values were either very high or very low.

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**Declaration of interest**

None declared.

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