Association of Different Transcranial Doppler-derived Indices of Cerebrovascular Dynamics With Delayed Cerebral Ischemia in Patients Suffering From Subarachnoid Hemorrhage: A Retrospective Study

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Abstract

Background

Cerebral vasospasm (VS) and delayed cerebral ischemia (DCI) constitute major complications following subarachnoid hemorrhage (SAH). A few studies have examined the relationship between different indices of cerebrovascular dynamics with the occurrence of VS. However, their potential association with the development of DCI remains elusive. In this study, we investigated the pattern of changes of different transcranial doppler-derived indices of cerebrovascular dynamics during vasospasm in patients suffering from subarachnoid hemorrhage, dichotomized by the presence of delayed cerebral ischemia.

Methods

A retrospective analysis was performed using recordings from 32 SAH patients, diagnosed with VS. Patients were divided in 2 groups, depending on development of DCI. Magnitude of slow waves (SWs) of cerebral blood flow velocity (CBFV) and arterial blood pressure was measured.

Cerebral autoregulation was estimated using the moving correlation coefficient Mxa. Cerebral arterial time constant (tau) was expressed as the product of resistance and compliance.

Results

In the whole population (N=32), magnitude of SWs of ipsilateral CBFV was increased during vasospasm (4.15 ± 1.55 vs before: 2.86 ± 1.21 cm/sec, $p < 0.001$). Ipsilateral SWs of CBFV before VS had higher magnitude in DCI group ($p < 0.001$) and were strongly predictive of DCI, with area under the curve = 0.745, $p = 0.009$. VS caused shortening of tau (ipsilateral to spasm: 0.17 ± 0.08 vs before: 0.25 ± 0.17 sec, $p = 0.04$) and interhemispheric asymmetry with lower values on ipsilateral side ($p < 0.01$). In patients with DCI (N=19), Mxa was increased during VS (ipsilateral to spasm: 0.36 ± 0.18 vs before: 0.26 ± 0.23, $p = 0.04$).

Conclusions

In the whole group of patients, VS was associated with increased CBFV SWs in both temporal and spatial assessments. Greater SWs before VS in DCI group, were strongly predictive of DCI.

Background

Cerebral vasospasm (VS) and delayed cerebral ischemia (DCI) constitute major complications following subarachnoid hemorrhage (SAH). DCI has been shown to occur in approximately 40% of patients suffering from SAH. It is more common in those who develop VS in large cerebral arteries, since arterial narrowing has a delayed onset with a peak between 5- and 14-days post ictus [1]. However, the maximum rate of DCI in patients with VS is around 50%, whereas up to one-third of patients with DCI do not exhibit large artery vasospasm [1,2]. In this respect, different studies have found that a combination of VS and dysfunction of cerebral autoregulation during the first 4-5 days post-SAH correlate with the occurrence of

DCI [3-5]. Such scenario is in accordance with Harper's dual-insult theory, which states that two hemodynamic insults, such as vascular spasm and autoregulatory failure, are needed to induce ischemia [6]. Nevertheless, such theory cannot explain why hypoperfusion can also be observed in areas not supplied by spastic arteries [7].

Different experimental studies have found that during the acute phase of SAH, global cerebral ischemia, blood-brain barrier disruption, cortical spreading depolarizations, microvascular spasm with endothelial dysfunction, as well as activation of an inflammatory cascade might contribute to increased tissue vulnerability to secondary insults [1,2,8]. It is unclear whether disturbed autoregulation is a consequence of such pathophysiological mechanisms. However, as has been suggested [7], loss of autoregulation is an ongoing and dynamic process with occasionally different mechanisms of origin. Thus, macrovascular spasm leads to distal compensatory vasodilatation with shortening of autoregulatory plateau which could signal impaired autoregulation upon testing, whereas microvascular spasm might induce a shift of the plateau to the right, towards higher arterial blood pressure (ABP) [7].

Surrogate markers of cerebral blood flow (CBF), such as transcranial doppler (TCD) cerebral blood flow velocity (CBFV), are frequently used to monitor development of VS, as well as integrity of autoregulation, through estimation of the dynamic changes that take place between ABP and CBFV in a frequency range of 'slow waves' (0.005 to 0.05 Hz) [9]. In this respect, different physiological parameters can be estimated, such as the index Mx evaluating the low frequency autoregulatory response [10], or other 'high frequency' components of autoregulation, like cerebrovascular time constant (tau), being a product of resistance (CVR) and compliance (Ca) [11-14]. Furthermore, other secondary indices describing cerebrovascular dynamics have been introduced, such as CBFV slow waves (SWs), which reflect dynamic oscillations in cerebral blood volume related to autoregulatory vasodilatation and vasoconstriction [15]. Finally, complexity analysis of TCD-derived CBFV signals has been applied for assessing a possible 'decomplexification' of cerebral circulation during different pathologic states [16,17].

The clinical significance of such indices has been tested in patients suffering from SAH, where shortening of tau [18] and both reduced [16] and gradually increasing complexity of CBFV [17], have been found in different studies, during VS. However, their potential relationship with the occurrence of DCI has not been evaluated yet. A few studies so far, have shown a significant association between unilateral autoregulatory failure and development of DCI [3-5]. In addition, the nature of SWs remains elusive since they have been observed in both healthy and pathologic states [15]. However, their absence has been associated with worse outcome in patients with traumatic brain injury (TBI) [15-19].

The primary aim of this study was to assess for the first time, how VS affects different TCD-derived parameters that describe both low- and high frequency components of cerebral autoregulation in patients after SAH, admitted to the Neurosciences and Trauma Critical Care Unit (NCCU), Department of Neurosurgery at Addenbrooke's Hospital, Cambridge, UK, with a special attention put into slow waves of blood flow velocity. SWs of both ABP and CBFV were measured in order to estimate the potential impact of VS upon their magnitude, as well as their relative changes. Secondly, we explored the potential

differences of VS-associated changes in cerebrovascular dynamics between subgroups of patients with and without DCI, in both temporal and spatial settings. Finally, we explored if there is any prognostic value of TCD-derived parameters related to the occurrence of DCI.

Methods

Study population

We retrospectively analyzed digitally recorded and prospectively collected data from patients admitted to the NCCU, Department of Neurosurgery at Addenbrooke's Hospital between June 2010 and January 2012 with a diagnosis of SAH, examined with TCD to assess state of autoregulation and detect VS [4,5]. Written consent and approval of the study was given by both patients and the local Addenbrooke's Research Ethics Committee, respectively.

Aneurysmal SAH was confirmed with either computed tomography (CT) or digital subtraction angiography (DSA). Out of 98 patients after SAH included in original studies [4,5], 32 conscious patients (mean age: 52.4 ± 10, 12 males and 20 females) who developed TCD-detected VS were included in our study. Study design is presented in Figure 1. Vasospasm was defined as mean blood flow velocity in the middle cerebral artery ($CBFV_{MCA}$) higher than 120 cm/sec and Lindegaard ratio (LR), which is the ratio between blood flow velocity of MCA and internal carotid artery (ICA), higher than 3 [20,21]. Median onset of VS was 6 days after SAH. Nineteen patients developed DCI within 21 days of ictus. DCI was defined as a drop of ≥ 2 points on the Glasgow coma scale (GCS) lasting more than 2 hours, after excluding intracranial hemorrhage, acute hydrocephalus, seizures, metabolic derangements or infection, with or without radiological signs of cerebral VS, as has been previously described [4,5,22]. Confirmation of DCI was made through imaging in unconscious patients [4,5].

All patients were treated with oral nimodipine 60 mg every 4h, whereas those we developed DCI received hypertensive, hypervolemic and hemodilutional therapy [23]. Neurologic status upon admission was assessed using GCS and the World Federation of Neurosurgical Societies (WFNS) scale, whereas modified Fisher scale was used for grading the amount of subarachnoid blood [24]. The Glasgow Outcome Scale (GOS) was used for assessing outcome at discharge from hospital.

Monitoring and data analysis

Arterial blood pressure was monitored non-invasively with Finapres 2300 (Ohmeda, Amsterdam, the Netherlands) via a finger cuff, with the hand kept at the heart level in all patients. Patients were supine with the head of the bed raised 30^0 to 45^0. In one patient ABP was monitored invasively from the radial arterial artery using a pressure monitoring kit (Baxter HealthCare, CA).

Bilateral TCD examinations of extracranial internal carotid arteries and MCA were performed, using 2MHz probes with Doppler Box (DWL Compumedics Germany). The raw data signals were recorded at sampling frequency of 100 Hz using ICM+ software (Cambridge Enterprise, Cambridge, UK,

https://icmplus.neurosurg.cam.ac. uk/). Mean values of signals were calculated averaging their values in a 10-second time window and then secondly averaging over the whole monitoring period (30-40 minutes). Only sessions with minimum of 30 minutes of simultaneous ABP and bilateral $CBFV_{MCA}$ recordings were included in the analyses.

Average measurements from 3 days of TCD recordings before and during VS, as well as differences between ipsilateral and contralateral to the VS sides were compared for all patients and between subgroups with and without DCI. Both location of VS on TCD and lateralization of ischemic symptoms were used for assessing hemispheric differences of various measured cerebrovascular properties. When bilateral VS was present, the analysis included averaging of both sides.

Calculation of different cerebrovascular parameters

Slow waves (SWs)

The magnitude of slow waves was assessed using spectral analysis of $CBFV_{MCA}$ and ABP waveforms and calculated as the square root of the power of the signal in the frequency range between 0.05 and 0.005 Hz [14], using ICM+ software. Artefacts were manually removed prior to analysis.

Cerebral arterial time constant (tau)

The time constant of cerebral arterial bed is a TCD-derived index indicating how fast 'arterial blood stabilizes after a change in ABP'[14,18]. In other words, it can reflect 'the time of the filling arterial bed distal to the level of insonated vessel, following cardiac systole'[14]. In that case, although $CBFV_{MCA}$ is measured within a large artery, tau describes the distal vascular network as the product of Ca and CVRa:

tau = Ca*CVRa =

$(AMP_{CaBV}*Sa/AMP_{ABP})*[mean\ ABP/(\ mean\ CBFV_{MCA} * Sa)]$ [sec] **equation 1**

where Sa is the cross-sectional area of the insonated vessel that can be ultimately omitted from the equation, CVRa is the resistance of small cerebral arteries and arterioles estimated using ABP instead of cerebral perfusion pressure, AMP_{CaBV} and AMP_{ABP} are the fundamental harmonic amplitudes of the pulse changes of cerebral arterial blood volume (CaBV) and ABP respectively, calculated using Fast Fourier transformation of their original time series. Pulsatile changes of cerebral arterial blood volume (ΔCaBV) can be estimated using the methodology first described by Avezaat and van Eijnhoven [25], where ΔCaBV during a cardiac cycle is calculated as an integral of the difference between arterial pulsatile inflow and venous outflow of cerebral blood [12,13]. Tau enables comparisons between different patients and allows for assessing whether alterations in compliance are balanced by changes in resistance and vice versa [12,14].

Mean velocity autoregulation index (Mxa)

The TCD-derived mean velocity index (Mx) can be measured for assessing cerebral autoregulation. It is calculated as a Pearson's moving correlation coefficient between 30 consecutive samples of averaged (over 10 seconds) cerebral perfusion pressure (CPP) and mean $CBFV_{MCA}$ with an update every 10 seconds [10]. In this study, ABP instead of CPP was measured, giving rise to the Mxa index. A passive transmission of ABP fluctuations to mean flow velocity reflects impaired cerebral autoregulation and therefore, the calculated Mxa will be positive. A zero or negative Mxa signifies none or inverse association between ABP and $CBFV_{MCA}$, something that is associated with preserved autoregulation [10]. In patients suffering from SAH, it has been suggested that values of Mxa during VS greater than 0.46 indicate impaired autoregulation [26].

Sample entropy (SampEn)

We applied SampEn as a measure of complexity of physiological time series [27]. Sample entropy represents the negative natural logarithm of the conditional probability that two sequences similar for m points remain similar at the next point (m + 1) with a tolerance r. The parameter r that is the tolerance for accepting matches, is usually set between 15-25% of standard deviation (SD) of the time series after normalization (SD=1). The parameter m (embedding dimension) is the length of sequences to be compared and its values is usually set to 1 or 2 for data length ranging from 100 to 5000 data points. In our analysis, we computed SampEn of $CBFV_{MCA}$ signals, using ICM+ software assigning the values of 2 for m and 0.15 for r.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 26 package (Armonk, NY, USA). Patients were dichotomized into DCI and non-DCI groups. The assumption of normal distribution was confirmed using Kolmogorov-Smirnoff test. The x^2 test was used for categorial variables. Temporal comparisons between TCD-derived indices before (pre-VS) and during VS, as well as spatial comparisons between ipsilateral and contralateral sides were performed using t-paired test for the overall group of patients. The t-test for independent samples was used for comparisons between groups with and without DCI. Values were averaged per monitoring session, before and during VS, based on the TCD onset of VS for each patient. Bivariate correlations between different measured variables were estimated using the Pearson r coefficient. Binary logistic regression and Receiver Operating Characteristic (ROC) curve analysis were applied for analyzing the potential association between measured parameters with development of DCI. Data are presented as mean ± SD, whereas the level of significance (p value) was set at 0.05.

Results

Table 1 summarizes the baseline characteristics for the included patients divided by the presence of DCI. The two cohorts did not differ in terms of age, WFNS and modified Fisher scales, GCS upon both admission and discharge, as well as GOS. ABP values did not differ significantly between pre VS and VS period of measurements, neither for the whole population nor between and within groups.

Ipsilateral mean CBFV values were significantly increased during VS in all patients (spasm: 156.2 ± 23.7 vs before: 89.6 ± 22.5 cm/sec, p < 0.001), as well as in both groups with and without DCI (spasm: 150.8 ± 33.2 vs before: 90.9 ± 25.5 cm/sec, p < 0.001 for DCI & 167.9 ± 33.7 vs 85.9 ± 22.4 cm/sec, p < 0.001 for non DCI group, respectively). However, they did not differ between groups significantly, neither before nor during spasm.

Differences of measured TCD-derived variables before and during VS for all patients, are presented in Table 2, whereas differences between groups with and without DCI are shown in Table 3.

Table 1. Characteristics of all patients and subgroups with and without DCI.

Variables	Overall (N=32)	DCI (N=19)	Non-DCI (N=13)	p value
Age, years ± SD	52.4 ± 10	54.15 ± 11.8	50 ± 7.6	0.27$
Sex (male/female)	12/20	8/11	4/9	0.74#
WFNS (mean)	2.37 ± 1.33	2.36 ± 1.38	2.38 ± 1.32	0.97#
Modified Fisher scale				
GCS admission	3 ± 0.8	3.2 ± 0.7	3.1 ± 1	0.94#
GCS discharge	12.2 ± 3.4	12.4 ± 3.2	11.9 ± 3.8	0.70#
GOS	13.8 ± 2.9	13.2 ± 3	14.1 ± 1	0.16#
Aneurysm location	4 ± 1	4 ± 1	4 ± 1	0.55#
1. AcomA				
2. MCA				0.53#
3. PcomA	9	6	3	0.93#
4. PICA	8	4	4	0.12#
5. BA	9	6	3	0.46#
6. ICA	4	2	2	0.35#
VS side	1	0	1	0.32#
1. Right	1	1	0	0.44#
2. Left				0.67#
3. Bilateral	14	9	5	0.72#
Clipping/coiling	11	6	5	0.40#
Rebleeding	7	4	3	0.32#
	20/12	12/7	8/5	
	1	0	1	

DCI: delayed cerebral ischemia, WFNS: World Federation of Neurosurgical Societies, GCS: Glasgow Coma Scale, GOS: Glasgow outcome scale, AcomA: anterior com-municating artery, MCA: middle cerebral artery,

PcomA: posterior communicating artery, PICA: posterior inferior cerebellar artery, BA: basilar artery, ICA: internal carotid artery, VS: vasospasm, SD: standard deviation, $^\$$:2-tailed t-test, $^\#$: x^2 test.

Table 2. Temporal (pre VS vs VS) and spatial (ipsilateral vs contralateral) differences of mean values of different measured parameters across the overall study population (N = 32, paired samples t-test).

Variables	Side of measurement	Pre VS	During VS	p value
CBFV SWs	ipsilateral	2.86 ± 1.21	4.15 ± 1.55	**< 0.001**
[cm/sec]	contralateral	2.89 ± 1.48	3.29 ± 1.3	0.73
	p value	0.92	**0.01**	
Tau	ipsilateral	0.25 ± 0.17	0.17 ± 0.08	**0.04**
[sec]	contralateral	0.28 ± 0.16	0.19 ± 0.09	0.50
	p value	0.32	**0.01**	
Mxa	ipsilateral	0.24 ± 0.20	0.31 ± 0.21	0.16
	contralateral	0.20 ± 0.18	0.23 ± 0.26	0.15
	p value	0.55	0.23	
SampEn	ipsilateral	2.67 ± 0.93	3.00 ± 0.96	0.15
	contralateral	2.95 ± 1.32	3.16 ± 2.15	0.15
	p value	0.63	0.70	

VS: vasospasm, Tau: time constant, CBFV SWs: cerebral blood flow velocity slow waves, Mxa: mean autoregulatory velocity index, SampEn: sample entropy.

Table 3. Temporal (pre VS vs VS) and spatial (ipsilateral vs contralateral) differences of mean values of different parameters between DCI and non-DCI groups of patients (t-test for independent samples).

Spatial comparisons during VS (ipsilateral vs contralateral)				
Variables	Side of measurement	DCI (N=19)	Non-DCI (N=13)	p value
Mxa	ipsilateral	0.36 ± 0.18	0.26 ± 0.23	**0.04**
	contralateral	0.21 ± 0.23	0.23 ± 0.32	0.52
	p value	**0.03**	0.62	

Temporal comparisons (ipsilateral pre VS vs during VS)

Variables	Time of measurement	DCI (N=19)	Non-DCI (N=13)	p value
CBFV SWs [cm/sec]	pre VS	3.20 ± 1.02	2.25 ± 1.08	**< 0.001**
	during VS	3.95 ± 1.45	4.64 ± 1.43	0.31
	p value	0.62	**< 0.001**	
Mxa	pre VS	0.23 ± 0.23	0.26 ± 0.16	0.52
	during VS	0.36 ± 0.18	0.26 ± 0.23	**0.04**
	p value	**0.04**	0.32	
tau (sec)	pre VS	0.31 ± 0.20	0.20 ± 0.09	0.42
	during VS	0.18 ± 0.09	0.17 ± 0.10	0.53
	p value	0.06	0.4	
SampEn	pre VS	2.6 ± 0.9	2.7 ± 0.9	0.8
	during VS	3.03 ± 1.01	2.9 ± 0.9	0.62
	p value	$p = 0.2$	$p = 0.8$	

VS: vasospasm, DCI: delayed cerebral ischemia, tau: time constant, CBFV SWs: cerebral blood flow velocity slow waves, Mxa: mean autoregulatory velocity index, SampEn: sample entropy.

Slow waves of CBFV and ABP

During VS, magnitude of SWs of CBFV was significantly increased related to pre VS measurements on the ipsilateral side (4.15 ± 1.55 vs 2.86 ± 1.21 cm/sec, $p < 0.001$, 95% CI: 0.72-2) for the whole studying population. Similar differences were found during spatial assessments (Table 2).

Ipsilateral CBFV SWs exhibited significant increase during VS in the non-DCI group compared to pre VS values (4.64 ± 1.43 vs 2.25 ± 1.08 cm/sec, $p < 0.001$, 95% CI: 1.55-3.22, Table 3, Figure 2). Moreover,

patients with DCI had significantly increased ipsilateral SWs before VS in relation with non-DCI group (3.20 ± 1.02 vs 2.25 ± 1.08 cm/sec, p < 0.001, 95% CI: 0.23-1.82).

On the contrary, SWs of ABP did not exhibit significant differences during VS, neither for the whole patients' population (before: 2.19 ± 1.42 vs spasm: 2.42 ± 1.26 mmHg, p = 0.29), nor within groups (before: 2.48 ± 1.31 vs spasm: 2.32 ± 0.81 mmHg, p = 0.62 for DCI & 1.93 ± 1.52 vs 2.32 ± 1.72 mmHg, p = 0.16 for non-DCI group, respectively). Finally, no differences between groups were found as well.

Tau, Mxa and SampEn

Ipsilateral tau during VS was significantly shortened in relation to pre VS period of measurements (p = 0.04, 95% CI: -0.003 to -0.16), as well as compared to contralateral side (p = 0.01, 95% CI: -0.004 to -0.35, Table 2). Nevertheless, when stratified by DCI, the ipsilateral difference did not reach significance (p = 0.06 for DCI group and p = 0.4 for non-DCI group, respectively, Table 3), whereas no differences were found between cohorts during both pre VS and VS periods of recordings.

Ipsilateral Mxa was greater during VS compared to pre VS values but differences were not statistically significant (p = 0.16, Table 2). On the contrary, when stratified by DCI, the ipsilateral Mxa was significantly increased during VS in DCI vs non-DCI groups of patients (p = 0.04, 95% CI: 0.03-0.23, Table 3). Furthermore, in pairwise comparisons, Mxa was significantly higher in both temporal and spatial assessments in the DCI cohort (Table 3).

Ipsilateral SampEn was greater during VS compared to pre VS values but differences were not statistically significant (p = 0.15, Table 2). In addition, ipsilateral SampEn was found to increase during VS in both DCI and non-DCI patients but without reaching statistical significance (p = 0.2 for DCI group and p = 0.8 for non-DCI group, respectively, Table 3). Finally, and similarly with tau, SampEn did not differ between cohorts during different times of measurements.

Bivariate correlations

A moderate negative correlation was found between ΔSW (SWs VS-pre VS) and ΔMxa (Mxa VS -Mxa pre VS) with Pearson r = - 0.37, p = 0.04, whereas CBFV SWs were also negatively correlated with tau during VS but at the limit of statistical significance (r = -0.35, p = 0.05). Finally, for all patients during VS, no correlation was found between ipsilateral mean CBFV and magnitude of CBFV SWs (r = 0.12, p = 0.6), whereas a positive correlation was found before VS for the DCI group (r = 0.7, p < 0.001).

Prediction of DCI

Patients who developed DCI during hospitalization exhibited increased ipsilateral pre VS CBFV SWs, which were found to predict development of DCI, as is depicted in Table 4. Thus, using the univariate results for variable selection, we found that one-unit change in pre VS SWs resulted in a 0.92-unit change in the log of the odds. ROC curve analysis found an area under the curve of 0.745 (p = 0.02, Figure 3).

Table 4. Binary logistic regression model for predicting DCI.

Parameter	B	SE	Wald	p value	OR	95% CI for OR
Pre VS CBFV SWs	0.92	0.44	4.33	0.03	2.52	1.05-6.02

VS: vasospasm, DCI: delayed cerebral ischemia, CBFV SWs: cerebral blood flow velocity slow waves, SE: standard error, CI: confidence intervals, OR: odds ratio.

Discussion

In the present study, we measured and compared different TCD-derived hemodynamic and complexity indices of cerebrovascular dynamics, in order to investigate their behavior during VS in patients after SAH, dichotomized by the presence of DCI.

For the whole group of patients, we observed that during VS, CBFV SWs were found to increase in relation to the pre VS measurements (paired temporal comparisons). Similar differences were found between ipsilateral vs contralateral side during VS (paired spatial comparisons). Moreover, our findings confirm that VS can cause a disturbance of autoregulation at the side of aneurysm [3-5]. We also confirm previous study by Kasprowicz and colleagues [18], who found that tau is significantly reduced during VS even before formal TCD signs of VS are observed, suggesting a potentially therapeutic window for escalation of treatment.

CBFV SWs with an associated frequency range of 0.005 to 0.05 Hz, reflect dynamic oscillations in cerebral blood volume related to autoregulatory vasodilatation and vasoconstriction [15]. Fluctuations of CBFV measured with TCD have been found to occur simultaneously with intracranial pressure (ICP) B-waves and occupy the same frequency [15,19.

The physiological and clinical significance of SWs remains debated since they do not only occur during pathologic conditions but have also been observed in healthy subjects [15]. Thus, pCO_2 changes related oscillations in the cerebrovascular volume, was believed to be one major mechanism of origin [28]. However, such theory does not seem to be universally advocated, since SWs have been also found in deeply sedated patients with stable pCO_2 levels under mechanical ventilation [29].

According to Rosner [30], SWs are related to plateau waves of ICP waveforms, since they are generated by the same mechanism. Thus, an unstable ABP or faster and greater ABP decrements, induce vasodilatation when autoregulation is intact. Subsequently and through a vasodilatory cascade, the increase in cerebral blood volume and ICP promotes through a Cushing response an increase in ABP, terminating the pressure waves.

Others have suggested that SWs are derived from rhythmic cerebral vasoconstriction caused by an intrinsic brain stem rhythm, since their occurrence is independent from changes in pCO_2 levels, ABP and

respiration [31]. In this respect, general anesthesia has been found to reduce amplitude of SWs of ICP [32].

Greitz and colleagues [33], have proposed a different mechanism of origin of SWs. They suggested that restricted arterial distensibility due to decreased intracranial compliance in cases of chronic hydrocephalus, is associated with increased capillary pulsations and subsequently, increased CBFV SWs.

Stefanovska and coworkers [34], analyzing fluctuations in human peripheral blood flow, recognized 5 distinct oscillations, with frequency intervals between 0.02-0.05 Hz reflecting smooth muscle autonomic innervation, where frequencies lower than 0.05 Hz were related to both local neurogenic and metabolic inputs. Particularly, endothelial activity reflected in the concentration of different molecules secreted from endothelial cells, with vasodilatory or vasoconstrictive properties, such as nitric oxide (NO) and endothelin respectively, contributed to oscillations of around 0.01 Hz. According to classic studies of Fry and Byrom [35,36], when cerebral arteries are narrowed, like in cases of VS, flow pulsations and wall shear stress will be enhanced, tending to increase the power dissipation and thus, the pressure gradient along the vascular tree. In this case, all sequential branches of the capillary network try to dilate in order to avoid or decrease this augmented pressure drop, through production of local vasodilatory molecules, such as NO. Such metabolic effects might be reflected in the amplitude of blood flow oscillations within a frequency range below 0.02 Hz.

Based on the previous discussion, we suggest that increased CBFV SWs during VS in both temporal and spatial assessments that was found in our study, correspond to increased capillary stress. In this case, stiffening of large conduit arteries due to VS might induce increased and faster pressure and volume transmission into the brain capillaries. Although VS is mainly associated with vessel narrowing, where volume transmission is not necessarily increased, we suppose that shortened tau might reflect acceleration of the volume transmission, which in association with increased flow rate might enhance wall shear stress in the capillary network distal to insonation site. In this respect, a negative correlation between tau and SWs during VS was found but at the limit of statistical significance. Consequently, and according to Stefanovska's findings, such effects could increase amplitude of oscillations below 0.02 Hz due to enhanced production of different vasodilatory molecules, as an endothelial response to augmented shear stress. In addition, lack of significant correlation between ipsilateral mean CBFV and SWs might reflect their dissociation due to vessel lumen narrowing during VS, whereas ABP SWs did not differ significantly from pre VS values. Such findings further support our suggestion that increased magnitude of SWs during VS is mainly attributed to local mechanisms related to capillary stress. Finally, triple H therapy cannot account for our results, since ABP values did not differ significantly between pre VS and VS period of measurements.

Another finding of this study was the negative correlation between ΔSW and ΔMxa during VS. In this case, disturbed autoregulation during VS (even if it did not reach statistical significance) seems to be associated with modest increase in SWs. It seems that a highly decreased vasomotor tone or even vasoparalysis due to dysautoregulation, reflected in increased Mxa values, is associated with loss of

pressure reactivity of cerebral blood vessels, limiting the ability of endothelial factors to induce oscillations in vessels' wall, with subsequent reduced amplitude of low frequency oscillations. Nevertheless, and since a significant stiffening of the arterial bed is also needed to explain our results, we assume that shortening of tau during VS partially reflects a decreased vascular compliance, as has already been suggested by Kasprowicz and colleagues [18].

Cerebral circulation can be considered as a complex system, since it involves both central and peripheral control mechanisms through multiple feedback loops [37]. Loss of complexity during illness might be attributed to altered coupling between system's components [38]. Decreased complexity reflects either decreased information content or decreased disorder, related to the number of 'microstates' that are accessible to the system [37].

Soehle and colleagues [16], evaluated variability and complexity of TCD-derived CBFV signals in patients suffering from SAH and found significantly reduced variability and complexity during VS, which was associated with unfavorable outcome. In addition, Placek and coworkers [17], using an index based on Renyi entropy, found that VS was associated with gradually increasing complexity of CBFV, attributed to a potential improvement in autoregulation and the number of regulatory mechanisms involved with its variability. In addition, complexity of blood flow was significantly reduced ipsilateral to aneurysm rupture related to contralateral side before occurrence of VS, suggesting, as in the case of tau, a potential therapeutic window.

In our investigation and similarly with Placek's study [17], SampEn was also reduced ipsilateral compared to contralateral side, both before and during VS, but without reaching statistical significance. Furthermore, ipsilateral SampEn during VS was non significantly increased in relation to pre VS measurements. We suggest that differences between methods for assessing complexity could be responsible for inconsistency across different studies.

Cerebral autoregulation estimated with Mxa was found to be significantly impaired during VS in patients who developed DCI related to pre VS measurements. Moreover, ipsilateral Mxa values during VS were significantly increased in DCI compared to non-DCI groups (temporal comparisons). Finally, patients with DCI exhibited a significant interhemispheric difference in autoregulation, since Mxa during VS was found to increase in the ipsilateral related to contralateral side of aneurysm rupture (spatial comparisons). Such findings are in keeping with previous studies [4,5], which showed that development of DCI was associated with a significant interhemispheric difference of autoregulation in the first 5 days after ictus.

Measurement of ABP rather than CPP for calculation of Mx might limit accuracy of our results. However, both Mx and Mxa have been shown to exhibit good correlation, particularly in cases of impaired autoregulation in TBI patients, although Mxa was not found to differ between patients with different outcome [39]. In this respect, our findings agree with those of Calviere and coworkers [3], who showed that the combination of both large artery VS and impaired autoregulation estimated with Mxa during the first 7 days from ictus, was correlated to subsequent DCI. Another potential confounder in our study

might be the arterial tension of pCO_2, limiting accuracy of comparisons between patients [40]. Nevertheless, none from our patients had a history of chronic obstructive pulmonary disease or any other pulmonary disease that might affect pCO_2 levels, assuming that its potential impact upon our measurements might be insignificant. In any case, our results agree with those from other studies where no arterial tension pCO_2 measurements were performed [3-5].

Ipsilateral CBFV SWs before VS were significantly increased in the DCI compared to the non-DCI cohort, whereas high ΔSW during VS was present only in patients who did not develop DCI. Since there are no similar studies in the literature, we can only guess about the potential pathophysiological mechanisms of such findings. Thus, we suggest that patients with DCI might experience an increased capillary stress even before the occurrence of VS; however, lack of differences between groups in terms of pre-VS values of Mxa or tau might signal different mechanisms of origin. Perhaps the increased heterogeneity of flow during the first days after SAH, which has been found in studies using direct perfusion methodology [41], suggest focal impairment of autoregulation that cannot be captured with TCD-derived indices. In this respect, a positive correlation was found between mean CBFV and SWs before VS in the DCI group, reflecting an association between SWs and fluctuations in CBF.

Furthermore, increased pre VS SWs could also be attributed to enhanced local neurogenic inputs originating in the brain stem, which are independent of the sympathetic nervous system [42]. Probably, in cases of highly focal disturbances of flow and autoregulation, inputs from the brain stem towards cerebral blood vessels are increased, in order to preserve CBF at the level of microcirculation. In such cases, magnitude of CBFV SWs will be augmented, since different local neurogenic mechanisms are also considered responsible for blood flow oscillations within a frequency range below 0.02 Hz [34]. In this respect, no differences were found between ABP SWs before and during VS, either between or within groups. Finally, ABP mean values were not different between groups. Thus, the association of high pre VS SWs with occurrence of DCI might reflect the significant predictive value of regional dysautoregulation. Nevertheless, these results need to be validated in a larger prospective study.

Finally, attenuated increase in CBFV SWs during VS in DCI patients related to non-DCI group, could be related to a state of vasoparalysis, since such condition may partially account for a reduction in blood vessels oscillatory capacity. Moreover, microvascular endothelial dysfunction and spasm could also be associated with lack of change in SWs during VS. Thus, experimental studies have found that cortical arterioles after VS due to SAH demonstrate attenuated dilation to different endothelial-dependent dilators, such as NO and adenosine diphosphate [43].

Some of the major limitations of this study is its retrospective nature, as well as the small sample size that might account for some of the negative associations found. Nevertheless, we included only conscious patients, in order to increase homogeneity of studied population, as well as to have clinically proven diagnosis of DCI, since its diagnosis in sedated subjects is more difficult and depends on different imaging techniques [23]. Moreover, the mixture of both sedated and conscious patients might dilute findings in terms of SWs changes [32]. In addition, mean CBFV did not differ between groups

significantly, both before and during spasm. Thus, our patients seem to have similar severity of VS, limiting its potential impact on our findings. Our results are in keeping with those from other investigators who evaluated relationships between different TCD-derived cerebrovascular parameters with outcome, in similar patients' groups. Non-invasive ABP measurement for Mx calculation through Finapres system could constitute another limitation in terms of accuracy of results. However, agreement between invasive and non-invasive assessment of Mx has been tested and a good correlation between the two methods was found [44].

Since TCD has limited spatial resolution, it is conceivable that regional disturbance of autoregulation, particularly affecting the posterior circulation might have been missed. Moreover, TCD cannot detect microvascular spasm, a potential mechanism of modest ΔSW increase during VS in DCI group.

In conclusion, we suggest that CBFV SWs even in the early days post ictus might help identify patients who are more susceptible to development of DCI throughout their hospital course. Moreover, simultaneous analysis of ICP and CBFV could enhance accuracy of measurements through estimation of CPP instead for ABP, whereas parallel monitoring of arterial tension of pCO_2 that affects thresholds of disturbed autoregulation might improve accuracy of comparisons between patients.

Conclusions

Slow waves of CBFV in DCI group were significantly higher before VS and predicted unfavorable outcome. Consequently, we suggest that following SAH, their daily monitoring through TCD measurements at the bedside, could improve understanding of complex physiology and eventually, optimize treatment.

Abbreviations

ABP: arterial blood pressure,

AMP: amplitude,

AUC: area under the curve,

CBF: cerebral blood flow,

CBFV: cerebral blood flow velocity,

Ca: compliance,

CPP: cerebral perfusion pressure,

CVR: cerebral vascular resistance,

DCI: delayed cerebral ischemia,

GSC: Glasgow Coma Scale,

GOS: Glasgow Outcome scale,

ICA: internal carotid artery,

ICP: intracranial pressure,

LR: Lindegaard ratio,

MCA: middle cerebral artery,

Mxa: mean velocity autoregulatory index,

ROC: Receiver Operating Characteristic,

SAH: subarachnoid hemorrhage,

SampEn: sample entropy,

SWs: slow waves,

tau: time constant,

TCD: transcranial Doppler,

VS: vasospasm,

WFNS: World Federation of Neurosurgical Societies scale.

Declarations

Ethics approval and consent to participate

This is a retrospective analysis of previously prospectively gathered data. For this type of study formal consent is not required.

However, written consent and approval of the previous studies including the same patients was given by both patients and the local Addenbrooke's Research Ethics Committee, respectively.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors except for MC and PS certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

MC and PS have financial interests in part of the licensing fees for the software ICM+ used in this project for data collection and analysis.

Authors' contributions

VP was the principal investigator who made the analyses and wrote the manuscript.

KB was the investigator who provided the data from previous prospective studies and edited the manuscript.

MP assisted to the software applications for data analysis and statistics.

ZC assisted to the software applications for data analysis and statistics and edited the manuscript.

PS assisted to the software applications for data analysis and statisticsand edited the manuscript.

MC assisted to the software applications for data analysis and statistics and edited the manuscript.

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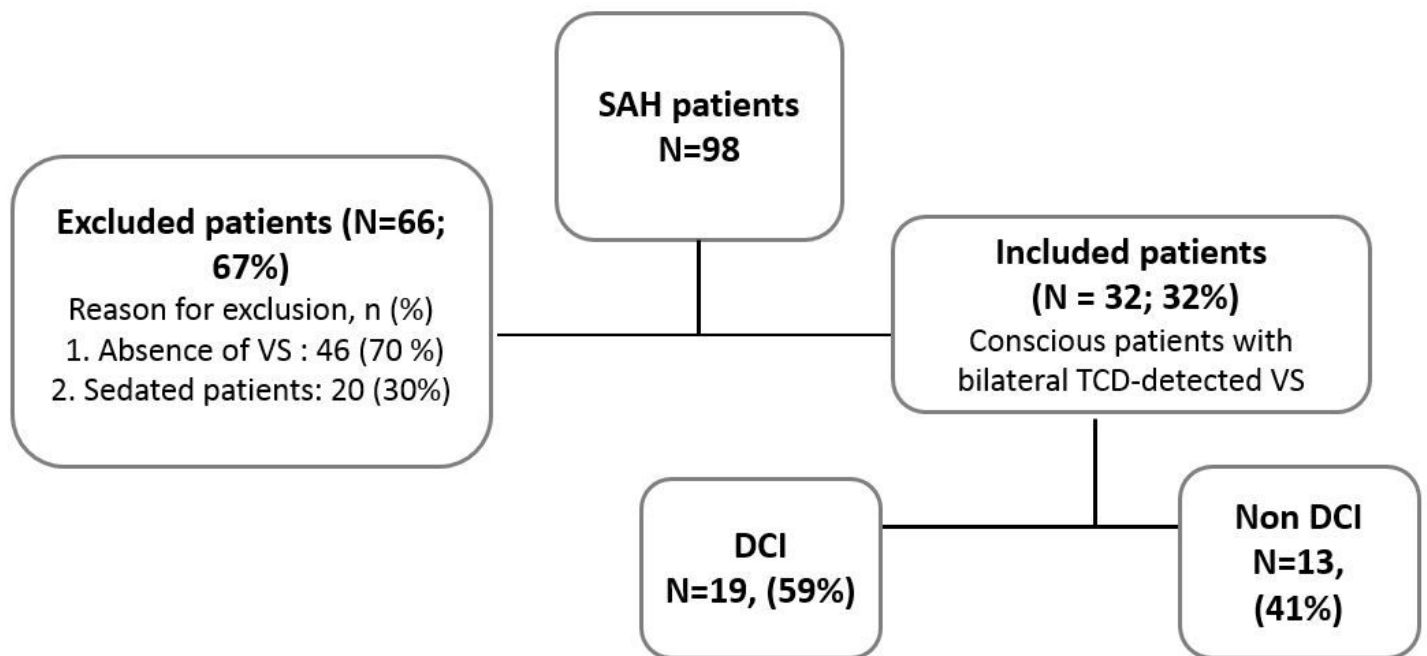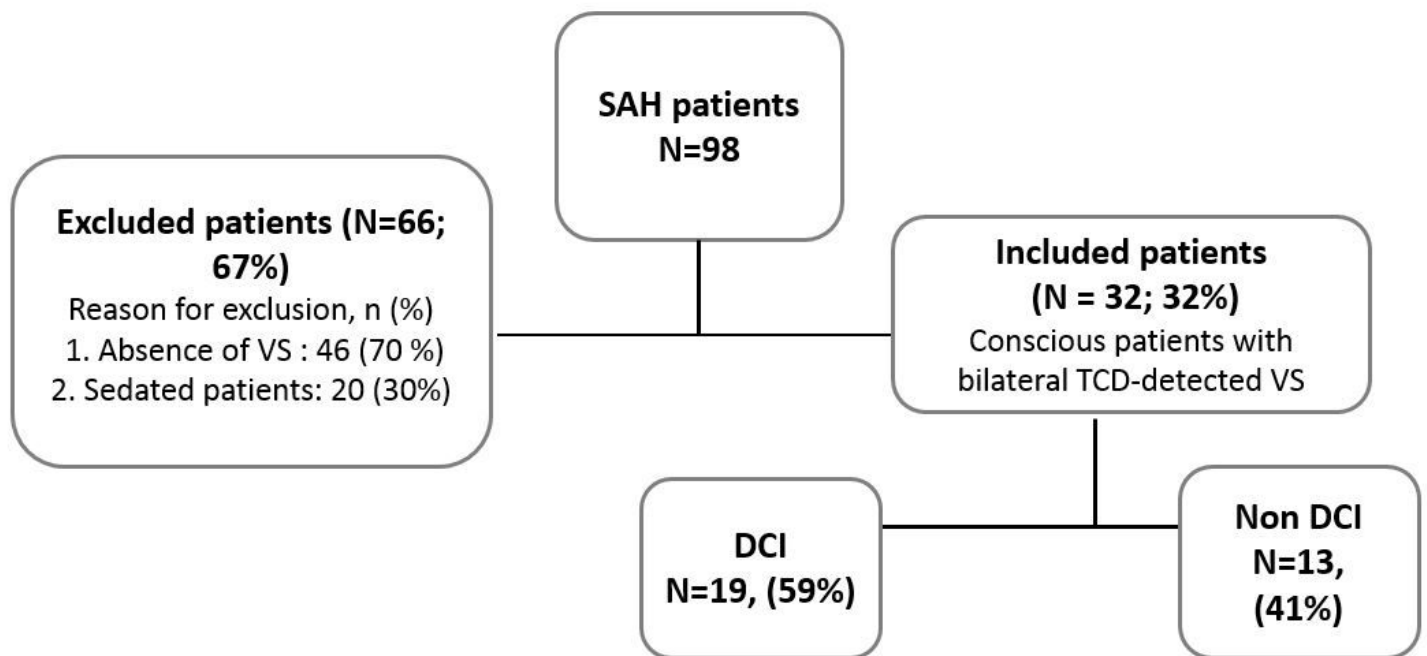
Figures

Figure 1

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Flow chart of the study. From a data base of 98 patients with SAH, 46 patients (70%) did not develop TCD-detected VS. Furthermore, from the remaining 52 cases with VS, 20 sedated patients were excluded from the study (30%). Included conscious subjects (N=32) were subsequently dichotomized in 19 patients who developed DCI vs 13 without DCI, within 21 of ictus.

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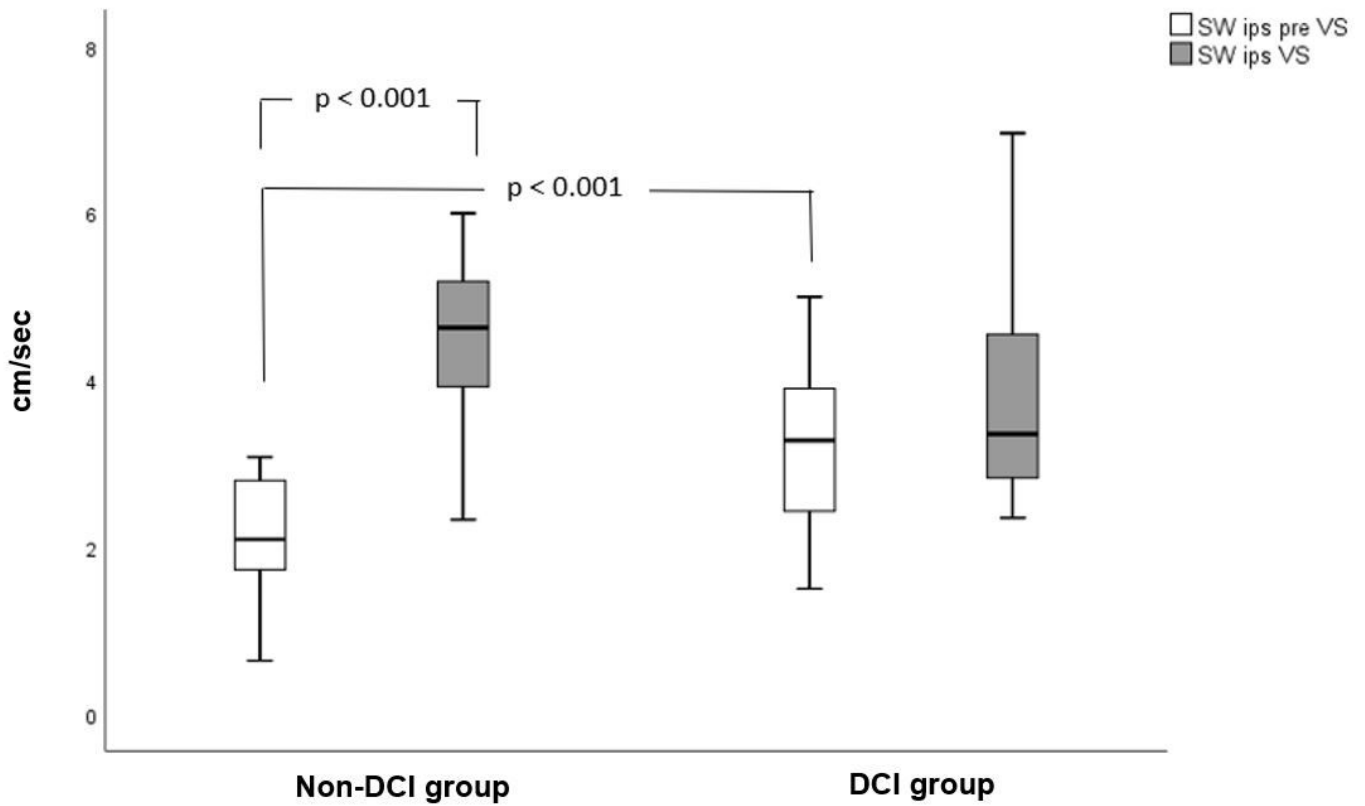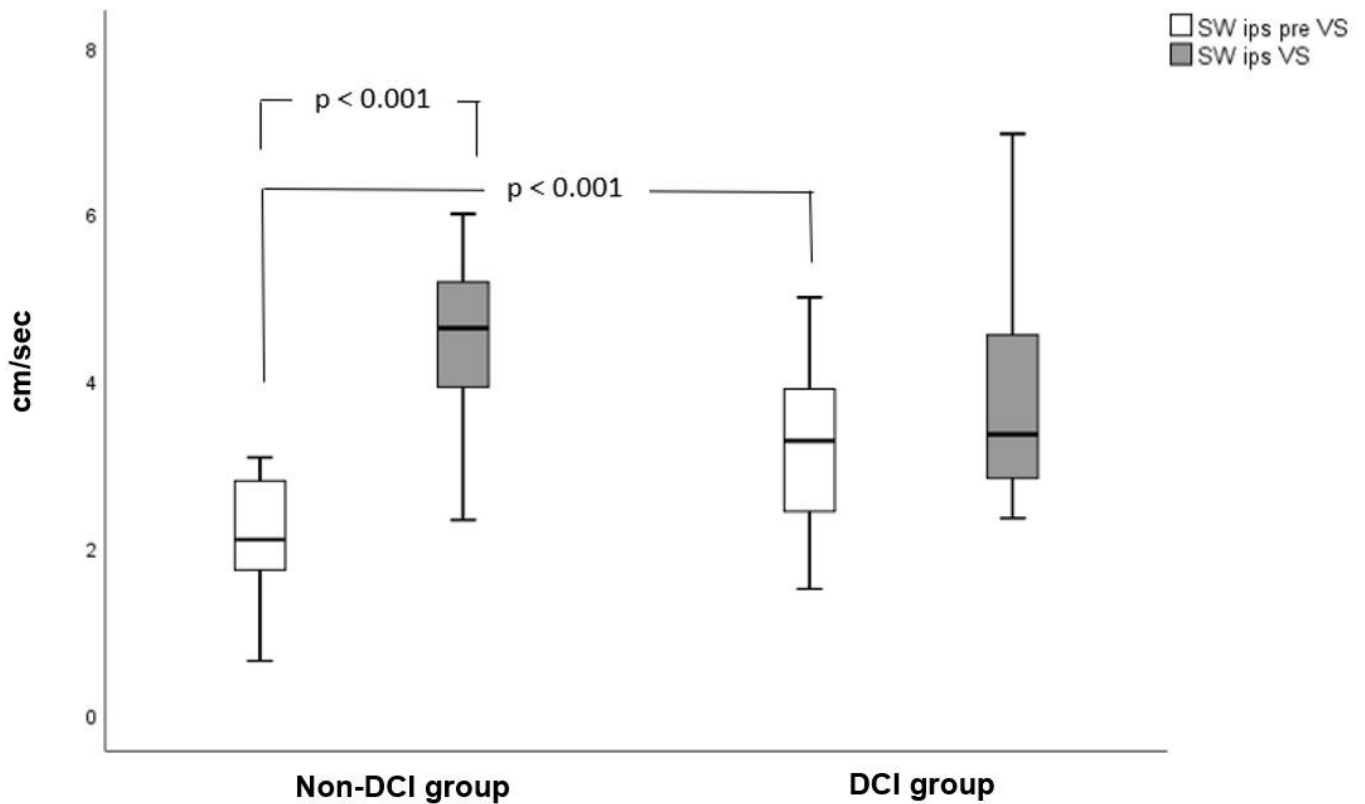
Figure 2

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Statistically significant differences of ipsilateral CBFV SWs before vasospasm (pre VS) are illustrated between delayed cerebral ischemia (DCI) and non-DCI groups, as well as between pre VS and during VS measurements within non-DCI group. Units of measurement in the y axis are cm/sec.

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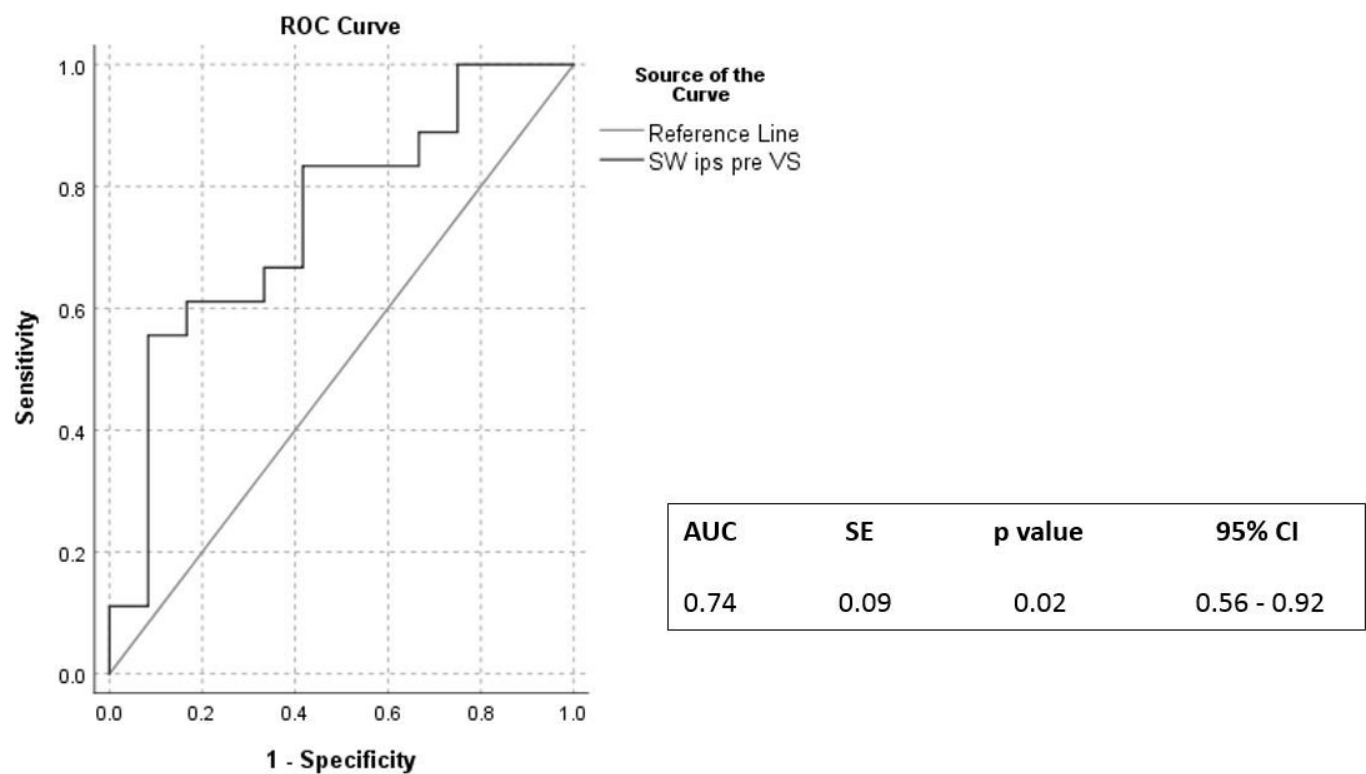| AUC	SE	p value	95% CI
0.74	0.09	0.02	0.56 - 0.92

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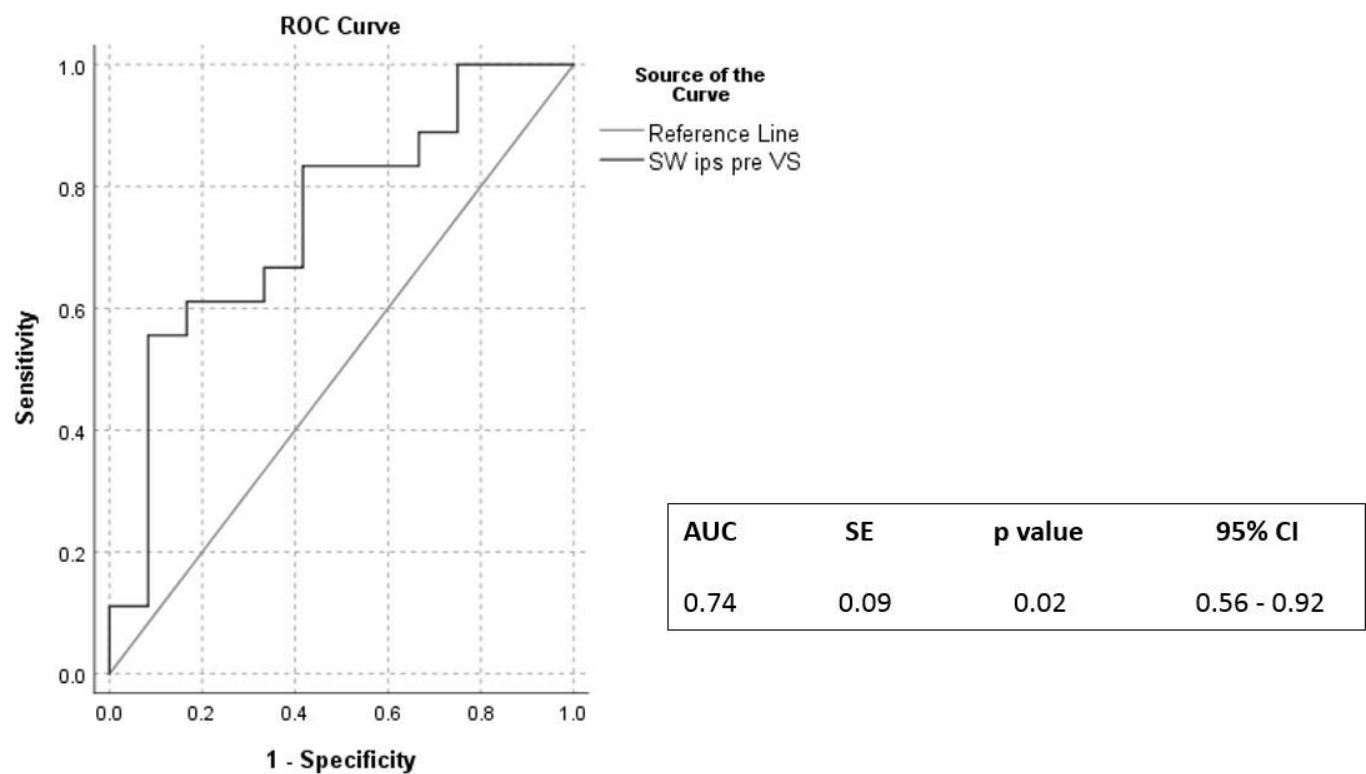| AUC	SE	p value	95% CI
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