

Periinterventional Vasospasm in Patients With Aneurysmal Subarachnoid Hemorrhage Predicts an Unfavorable Clinical Course

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BACKGROUND: Preliminary evidence exists that ultra-early angiographic vasospasm (UEAV) after aneurysmal subarachnoid hemorrhage (SAH) is associated with delayed cerebral vasospasm (DCVS), delayed cerebral ischemia (DCI), and poor functional outcome. Typically, detection of UEAV has been based on admission radiological imaging.

OBJECTIVE: To elucidate the occurrence of the phenomenon of UEAV during treatment in SAH patients.

METHODS: A total of 206 consecutive patients underwent either endovascular or microsurgical treatment in a hybrid operating room within 48 h after SAH. Time to DCVS and DCI, and poor functional outcome (both binary) were analyzed using Cox proportional-hazards and logistic regression models. We examined both univariable models (admission and periinterventional UEAV) and multivariable models (backward variable selection, including further known and suspected risk factors).

RESULTS: For UEAV detected in 33 patients (16%), 10 were admission and periinterventional and 23 periinterventional only. Both admission and periinterventional UEAV significantly increased the risk of DCVS (hazard ratio [HR] 1.7, 95% confidence interval [CI] 1.2–2.3, $P = .001$), DCI (odds ratio [OR] 5.9, CI 1.7–25.1, $P = .001$), and poor functional outcome (OR 4.7, CI 1.7–13.4, $P = .004$). Clipping, female sex, and higher Barrow Neurological Institute (BNI) scale increased the hazard for DCVS and the probability for DCI, whereas increasing patient age, poor initial World Federation of Neurological Surgeons (WFNS) grade, and intraparenchymal hemorrhage increased the probability for poor functional outcome.

CONCLUSION: Detection of admission or periinterventional UEAV poses high risk of DCVS, DCI, and poor outcome after SAH. Therefore, periinterventional UEAV should be considered an important warning sign that warrants both early monitoring and aggressive therapy.

KEY WORDS: Subarachnoid hemorrhage, Computed tomography, Digital subtraction angiography, Ultra-early angiographic vasospasm, Coiling, Clipping, Hybrid operating room, Delayed cerebral vasospasm, Delayed cerebral ischemia, Functional outcome

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Aneurysmal subarachnoid hemorrhage (SAH) is a life-threatening condition with a high overall 30-d case fatality rate of nearly 50%.¹ Strong prognostic determinants of outcome after SAH include age, initial clinical presentation, amount of SAH on admission computed tomography (CT) scan, delayed cerebral vasospasm (DCVS), and delayed cerebral ischemia (DCI). More recently, ultra-early angiographic vasospasm (UEAV), defined as cerebral arterial narrowing within

the first 2 d after SAH, has gained more attention as a potential early prognostic indicator for DCVS, DCI, and poor functional outcome.

Although UEAV is a well-known phenomenon that occurs in approximately 10% of all SAH patients, pathophysiological mechanisms and clinical importance are understudied.^{2–8} UEAV is not routinely recorded and its relative importance in the disease course after SAH is still highly debated.^{3–5,8} Of the 4 studies

that investigated an association between UEAV and DCVS, only 2 studies have reported the method of UEAV detection,^{3,5} one study evaluated the severity and duration of DCVS,⁵ and no study has yet investigated the temporal course of DCVS in the context of UEAV.

Toward addressing these gaps in the literature, we evaluated the clinical relevance of the phenomenon of UEAV in a cohort of our SAH patients with confirmed vasospasm either at the time of admission or during their intracranial aneurysm (IA) treatment itself. We then further determine the influence of UEAV on DCVS onset and its time course.

METHODS

Patients in this study were recruited from our institutional prospective cohort of patients with aneurysmal SAH between 2010 and 2016. Patients were at least 18 yr old and had confirmed SAH from a saccular IA diagnosed by computed tomography angiography (CTA) and digital subtraction angiography (DSA). We then identified those who underwent either craniotomy and IA clipping in a hybrid operating room with intraoperative DSA or endovascular coiling within 48 h of the ictus. The study was approved by our institutional review board and the Swiss ethics commission (EKNZ Nr.2017-00690). In accordance with the local regulations, no retrospective consent had to be obtained due to the disproportionate effort concerning the number of patients included.

Clinical Management

After referral to our emergency department, the diagnosis of SAH was confirmed by admission CTA or lumbar puncture. Acute symptomatic hydrocephalus was treated with an external ventricular drainage. All patients routinely underwent further assessment of their IA by 3-dimensional DSA. After reviewing each case for IA angioarchitecture, location, patient condition, and resources, our interdisciplinary cerebrovascular team recommended surgical or endovascular treatment.⁹ All patients were treated in our neurocritical care unit according to the guidelines of the American Heart Association and European Stroke Organization.^{10,11} Perfusion CT was routinely performed within 24 h after IA treatment and on day 7 after SAH.

Data Collection

Patient characteristics recorded at admission included age, sex, history of arterial hypertension, history of previous SAH, smoking status, admission Glasgow Coma Scale (GCS), initial clinical grade according to Hunt and Hess¹² and World Federation of Neurological Surgeons

(WFNS) grade, presence of neurological and cranial nerve deficit, and need for insertion of an external ventricular drain or lumbar drainage. On CT, we noted any intraparenchymal or intraventricular hemorrhage and graded the extent of SAH using the Fisher¹³ and Barrow Neurological Institute (BNI)¹⁴ scales. Maximal IA diameter and localization of the ruptured IA were evaluated on admission CTA, or admission DSA, or both.

Identification of UEAV was determined by the initial CTA or DSA and on periinterventional DSA (intraoperative DSA during clipping or coiling).¹⁵⁻¹⁷ Perinterventional UEAV was immediately treated with topical vasodilators and cerebral perfusion pressure augmentation. For a 21-d period, DCVS was screened daily by clinical observation and transcranial Doppler ultrasound. Patients underwent CTA or DSA if either clinical deterioration (not explained by other causes of neurological worsening) or increased Doppler velocity (mean flow >150 cm/s) occurred within days 3 to 21 after SAH. DCVS was defined as radiological evidence of cerebral vessel narrowing (at least >25% of baseline imaging) with corresponding neurological findings. Severity of UEAV was defined by arterial narrowing graded as mild (<25%), moderate (25%-50% narrowing), or severe (>50%). DCI was defined as evidence of hypodensities (not attributable to intracerebral hemorrhage or IA treatment) on CT scan at clinical follow-up 6 wk post SAH. All neuroradiological images were reviewed by B.B., who was blinded for clinical information; any case of uncertainties was discussed with a senior neuroradiologist (L.R., M.D.). Poor outcome was defined as modified Rankin Scale (mRS) 4 to 6 at 3 mo after SAH.¹⁸ The study protocol is given in Figure 1.

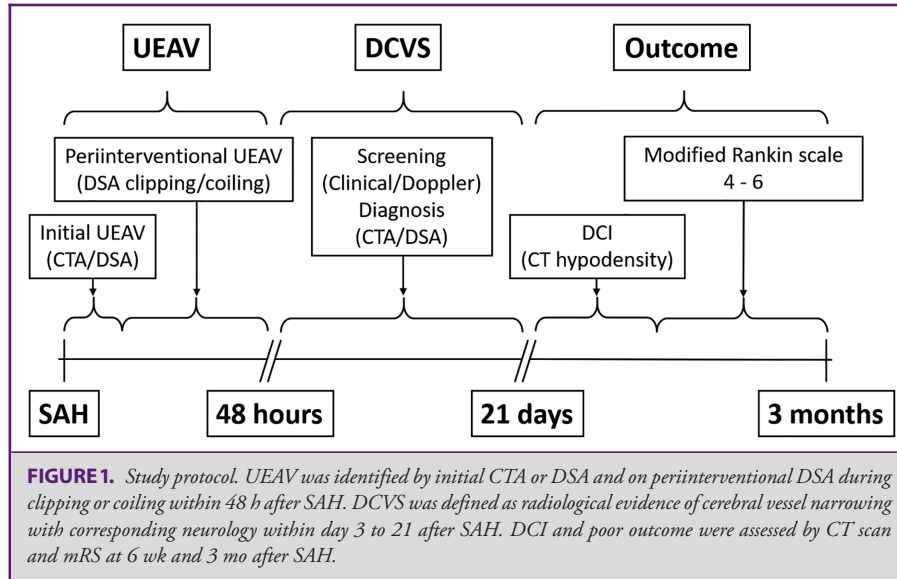
Statistical Analysis

Statistical analyses were conducted with the statistical software package R (RCoreTeam2017, Vienna, Austria), using two-sided statistical tests and a significance level of 0.05. Baseline patient and clinical characteristics were compared between groups using the Kruskal-Wallis and Wilcoxon rank sum tests for continuous variables, and Fisher's exact test for categorical variables.

The primary endpoint, time to DCVS, was analyzed by means of Cox proportional-hazards (PH) models. For patients without any event within the follow-up period, the primary endpoint was censored at 21 d. Patients who died within 3 to 21 d without delayed vasospasm were censored at their time of death. UEAV was used as a binary predictor (any UEAV, periinterventional with or without admission UEAV), vs no UEAV. The secondary binary endpoints, DCI and poor functional outcome, were analyzed by means of logistic regression models.

A backward model-selection procedure based on the Akaike information criterion (AIC) was performed to examine the association of the primary and secondary endpoints with UEAV, type of intervention (coiling vs clipping), and the following a priori defined, known, or suspected risk factors: age at SAH (continuous), sex, history of hypertension, history of SAH, high WFNS grading (grades 4-5 vs 1-3), neurological deficit at admission, cranial nerve deficit at admission, BNI grading scale (continuous 1-5), intraventricular hemorrhage, intraparenchymal hemorrhage, location of aneurysm (anterior [internal carotid artery (ICA)/anterior cerebral artery (ACA)/anterior communicating artery (AComA)/middle cerebral artery (MCA)/posterior communicating artery (PComA)] vs posterior [basilar artery (BA)/posterior cerebral artery (PCA)/vertebral artery (VA)/posterior inferior cerebellar artery (PICA)/superior cerebellar artery (SCA)]), and aneurysm size ≥ 10 mm. First, the full model, including all predictors, was fitted.

ABBREVIATIONS: **ACA**, anterior cerebral artery; **AComA**, anterior communicating artery; **AIC**, Akaike information criterion; **BNI**, Barrow Neurological Institute; **CI**, confidence interval; **CT**, computed tomography; **CTA**, computed tomography angiography; **DCI**, delayed cerebral ischemia; **DCVS**, delayed cerebral vasospasm; **DSA**, digital subtraction angiography; **GCS**, Glasgow Coma Scale; **HR**, hazard ratio; **IA**, intracranial aneurysm; **ICA**, internal carotid artery; **MCA**, middle cerebral artery; **OR**, odds ratio; **PComA**, posterior communicating artery; **PH**, proportional hazards; **SAH**, subarachnoid hemorrhage; **UEAV**, ultra-early angiographic vasospasm; **WFNS**, World Federation of Neurological Surgeons



Only main effects, that is, no interaction terms, were considered. The complexity of the full model was then reduced by removing single predictors in order to minimize the AIC as far as possible (ie, backward model selection). This resulted in the most parsimonious final model with a minimal AIC. For the final models, the hazard ratios (HRs) and respective odds ratios (ORs) are reported with 95% CIs, Z-value, and P-value for each predictor.

All statistical analyses were a priori defined in a statistical analysis plan. Sample size estimation was not performed but was determined based on the amount of available data.

RESULTS

Of a total of 268 patients evaluated for aneurysmal SAH, the 206 patients included underwent either craniotomy and IA clipping in a hybrid operating room with intraoperative DSA or endovascular coiling within 48 h of the ictus. Among these 206 patients, 33 were affected by UEAV and 173 were not. The 62 patients excluded consisted of 1 patient <18 yr, 1 patient whose aneurysm was wrapped, 36 patients who received no IA treatment because of poor clinical condition or death, and 24 patients in good clinical condition but excluded for late admission (>2 d after the presumed ictus). Worse clinical and radiological grades at admission, presence of intraparenchymal hemorrhage, and need for external ventricular drainage were more often observed among patients with UEAV. For other baseline clinical characteristics, no evidence of differences between the groups with or without UEAV was found (Table 1). In cases with periinterventional UEAV, we found no differences in the baseline characteristics, except for aneurysm location, between patients who had coiling or clipping (Table 2).

Among 206 patients included, UEAV affected 33 (16%) patients. For these 33 patients, UEAV was detected in 10 patients

on admission and during the intervention and in 23 patients solely during the intervention (5% and 11% of 206 patients, respectively) (Figures 2 and 3). DCVS developed a median of 5 d after SAH in 16 (70%) of the 23 patients with only periinterventional UEAV, and a median of 6 d after SAH in 84 (49%) of 173 patients without UEAV (Figure 4). Severity of UEAV neither significantly influenced the time course of DCVS nor impacted the assessed outcome measures. Periinterventional UEAV was recorded in 9 (9%) of 102 patients who underwent coiling and in 14 (14%) of 104 patients who underwent clipping.

Patients with UEAV were significantly more likely to develop DCVS (HR 1.64, 95% CI 1.02–2.62, $P = .041$; Table 3). The hazard for DCVS was further increased by aneurysm clipping compared with coiling (HR 1.96, 95% CI 1.30–2.94, $P = .001$). Moreover, the hazard for DCVS significantly increased for females and higher BNI score but decreased for intraparenchymal hemorrhage (Table 3). Patients with UEAV were nearly 6 times more likely to have DCI compared to patients without admission or periinterventional cerebral vasoconstriction (HR 5.87, 95% CI 1.69–25.09, $P = .009$). The odds were also significantly increased by clipping, female sex, poor WFNS, and increasing BNI scale (Table 4). Compared to those without UEAV, poor outcome was more than 4 times likely to occur in patients with UEAV (HR 4.65, 95% CI 1.66–13.43, $P = .004$). No association was found for type of intervention (clipping or coiling; predictor not selected in the final model). However, the odds for poor outcome were significantly increased for patients with poor WFNS, increasing age, and intraparenchymal hemorrhage (Table 5).

DISCUSSION

Our study examines for the first time the phenomenon of UEAV during endovascular and surgical treatment of ruptured

TABLE 1. Characteristics of 206 Patients Who Underwent Either Endovascular Therapy or Microsurgical Treatment in a Hybrid Operating Room Within 48 Hours After SAH and Comparison of Those Without UEAV or Those With UEAV Detected at Admission, Periinterventional, or Both

Variable	No UEAV	Initial and periinterventional UEAV	Periinterventional UEAV only	P
n	173	10	23	
Age at ictus (yr)	54.2 [47.4, 64.3]	51.5 [44.0, 63.5]	51.9 [47.6, 53.6]	.190
Female sex	121 (69.9)	8 (80.0)	16 (69.6)	.792
Hypertension	62 (35.8)	3 (30.0)	6 (26.1)	.623
Previous SAH	13 (7.5)	0 (0.0)	0 (0.0)	.266
Smoking	44 (78.6)	3 (100.0)	2 (100.0)	.513
Initial GCS	14 [10, 15]	8.0 [4, 14]	13 [8, 14]	.060
WFNS	2 [1, 4]	4.5 [2.5, 5.0]	2 [2, 4]	.047
Hunt and Hess	2 [2, 3]	4.0 [2, 5]	3 [2, 4]	.047
Initial neurological deficit	60 (34.7)	5 (50.0)	9 (39.1)	.583
Initial cranial nerve deficit	58 (33.5)	7 (70.0)	11 (47.8)	.035
Fisher scale	4 [3, 4]	4 [4, 4]	4 [4, 4]	.026
BNI scale	3 [2, 4]	5 [4, 5]	4 [3, 5]	.001
Intraventricular hemorrhage	106 (61.3)	8 (80.0)	17 (73.9)	.269
Intraparenchymal hemorrhage	37 (21.4)	7 (70.0)	8 (34.8)	.001
External ventricular drain (EVD)	76 (43.9)	6 (60.0)	16 (69.6)	.050
Lumbar drain	39 (22.8)	1 (10.0)	8 (36.4)	.216
Mean IA diameter (mm)	6.0 [4.6, 8.0]	7.2 [5.6, 9.7]	6.2 [5.0, 10.4]	.384
IA diameter ≥ 10 mm	25 (14.5)	3 (30.0)	6 (26.1)	.184
Posterior localization	16 (9.3)	1 (10.0)	4 (17.4)	.486
Localization				.578
ICA	18 (10.5)	1 (10.0)	1 (4.3)	
ACA	11 (6.4)	1 (10.0)	1 (4.3)	
ACoM	63 (36.6)	0 (0.0)	9 (39.1)	
MCA	36 (20.9)	6 (60.0)	5 (21.7)	
PCoM	28 (16.3)	1 (10.0)	3 (13.0)	
BA	9 (5.2)	1 (10.0)	3 (13.0)	
PCA	1 (0.6)	0 (0.0)	0 (0.0)	
VA	1 (0.6)	0 (0.0)	0 (0.0)	
PICA	2 (1.2)	0 (0.0)	1 (4.3)	
SCA	3 (1.7)	0 (0.0)	0 (0.0)	

Continuous variables are summarized by median [interquartile range] and compared between groups using the Kruskal-Wallis test; categorical variables are summarized by frequency (percentages) and compared between groups using Fischer's exact test.

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TABLE 2. Baseline Characteristics in 33 Patients With Periinterventional UEAV

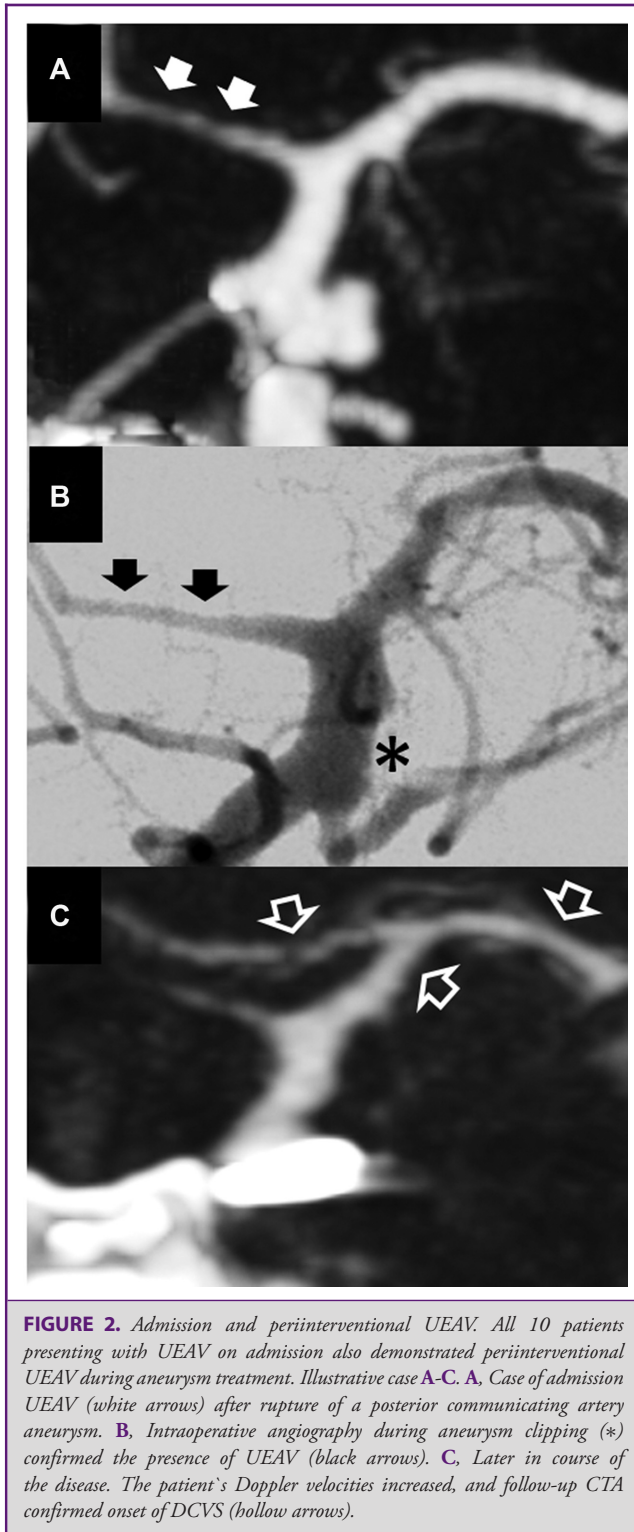
	Clipping	Coiling	P
N	19	14	
Age at ictus (yr)	52.3 [47.6, 54.9]	51.5 [44.6, 53.7]	.689
Female sex	16 (84.2)	8 (57.1)	.183
Hypertension	3 (15.8)	6 (42.9)	.183
Previous SAH	0 (0.0)	0 (0.0)	n/a
Smoking	3 (15.8)	2 (14.3)	1
Initial GCS	13.0 [7.5, 14.0]	11.0 [3.8, 14.8]	.882
WFNS	3.0 [2.0, 4.5]	4.0 [1.2, 5.0]	.895
Hunt and Hess	3.0 [2.0, 5.0]	3.5 [2.0, 4.0]	.866
Initial neurological deficit	7 (36.8)	7 (50.0)	.690
Initial cranial nerve deficit	10 (52.6)	8 (57.1)	1
Fisher scale	4.0 [4.0, 4.0]	4.0 [4.0, 4.0]	.797
BNi scale	5.0 [4.0, 5.0]	4.0 [3.2, 5.0]	.505
Intraventricular hemorrhage	13 (68.4)	12 (85.7)	.463
Intraparenchymal hemorrhage	10 (52.6)	5 (35.7)	.541
EVD	13 (68.4)	9 (64.3)	1
Lumbar drain	4 (21.1)	5 (38.5)	.499
Mean IA diameter (mm)	6.6 [4.6, 10.4]	6.6 [5.5, 9.5]	.743
IA diameter \geq 10 mm	5 (26.3)	4 (28.6)	1
Localization			.009
ICA	1 (5.3)	1 (7.1)	
ACA	1 (5.3)	1 (7.1)	
ACoM	6 (31.6)	3 (21.4)	
MCA	10 (52.6)	1 (7.1)	
PCoM	0 (0.0)	4 (28.6)	
BA	0 (0.0)	4 (28.6)	
PICA	1 (5.3)	0 (0.0)	
UEAV severity			.134
Mild	5 (26.3)	8 (57.1)	
Moderate	6 (31.6)	4 (28.6)	
Severe	8 (42.1)	2 (14.3)	

Continuous variables are summarized by median [interquartile range] and compared between groups using the Kruskal-Wallis test; categorical variables are summarized by frequency (percentages) and compared between groups using Fischer's exact test.

intracranial aneurysms. The findings provide evidence that periinterventional UAEV is a novel independent predictor for DCVS after SAH. Compared to those without vasospasm, patients with UEAV developed DCVS more often and earlier and were more likely affected by DCI and poor outcomes.

Pathophysiology of UEAV

The exact pathophysiological mechanism of UEAV remains unknown. Although acute vasoconstriction is a well-known phenomenon in experimental SAH, it is poorly recognized in



human cerebral vessels, which contract less when exposed to blood.¹⁹⁻²³ SAH-associated acute vasoconstriction in humans has been documented in aneurysm rupture during angiography.²² The International Cooperative Study on the Timing of Aneurysm Surgery reported for the first time in 1990 that 11% of SAH patients presented with admission cerebral vasospasm within a 72-h interval from SAH.^{6,24} However, the clinical significance and prognostic value of these UEAVs were long underestimated. Only after the retrospective analysis of the Tirilazad Mesylate data in 1999 and 2004 was UEAV acknowledged to be predictive of DCI and poor outcome after SAH.^{4,8} Two more recent studies confirmed these correlations and additionally reported a strong relation between UEAV and incidence of severe and treatment refractory DCVS.^{3,5} Our results are consistent with the pooled analysis of these 4 previous studies on the subject by demonstrating a significant association of UEAV with DCVS, DCI, and unfavorable outcome at follow-up.⁷

Studies that provide time-to-event data are rare. Al-Mufti et al. reported that the mean time to develop DCI was shorter in patients presenting with UEAV than those without.³ In a retrospective study of 531 patients, Jabbarli et al. identified that UEAV strongly correlated with severity and duration of DCVS.⁵ We found that the median time to DCVS onset was shorter in patients with UEAV after SAH. All these findings point to the high risk of in-hospital complications in UEAV patients.

Pathogenesis of Perinterventional UEAV

Although catheter-induced vasospasm during neuroendovascular procedures is a well-known phenomenon, there are limited data about the incidence and risk factors.^{25,26} The situation is similar to direct manipulation of the inner or outer cerebral artery during IA treatment. It is a known trigger of acute vasoconstriction, but the importance of periinterventional UEAV after SAH is poorly defined.²⁷⁻²⁹ Thanks to the routine use of intraoperative angiography during IA clipping, we learned that therapy-induced vasospasm is more often encountered in patients with SAH than those without.²⁸ This finding could be explained by increased reactivity of cerebral vessels due to SAH.³⁰ It is interesting to note that the phenomenon was documented more often during clipping than coiling. A possible explanation might be the increased mechanical vessel manipulation during open microsurgical IA occlusion compared with endovascular therapy. However, dissection and temporary clipping of sensitive arteries per se seem not to be associated with worsening of DCVS or increased risk of DCI after SAH.^{29,31}

Intracerebral hematoma, intraventricular bleeding, ruptured aneurysm size > 12 mm, and middle cerebral artery location were significantly more likely in patients with UEAV.⁷ Likewise, we more often found intracerebral hematoma, and high Fisher

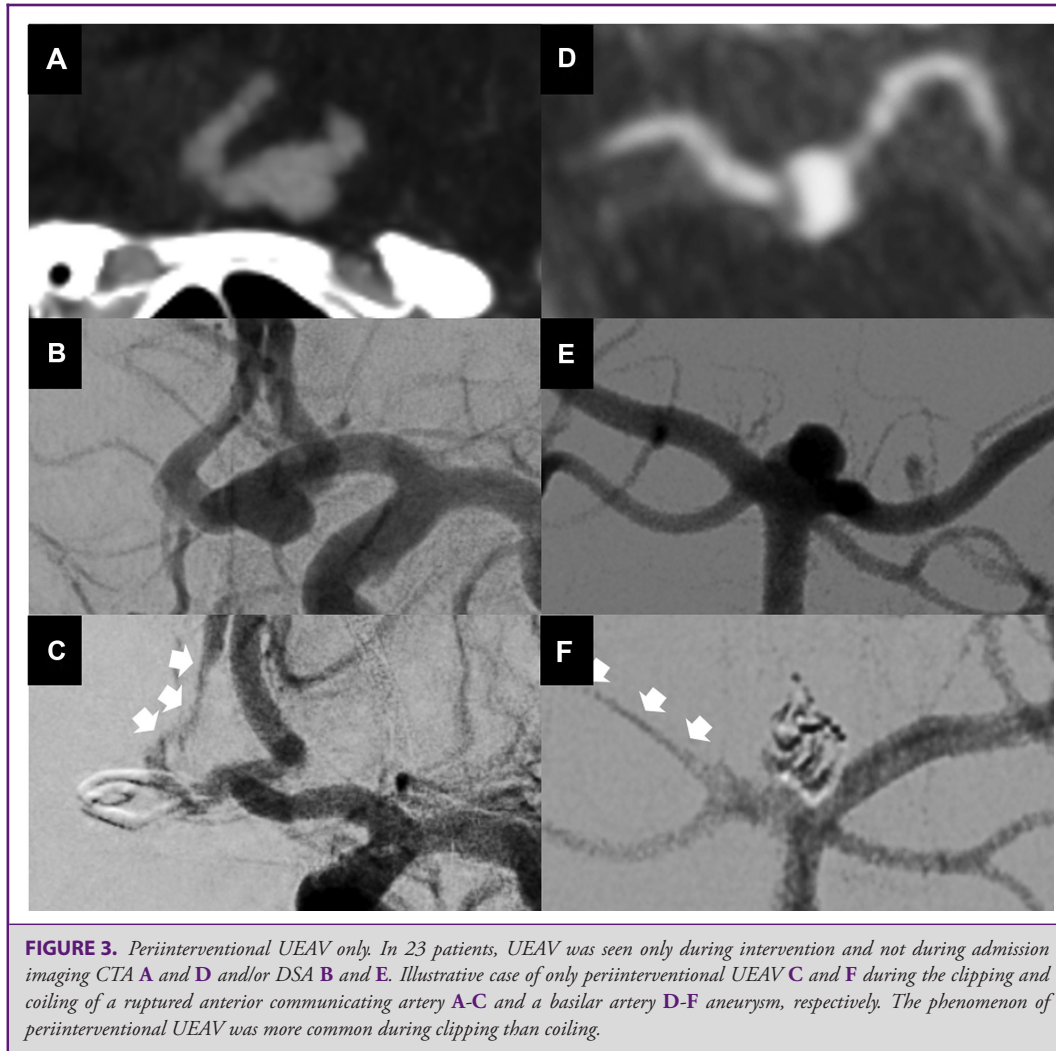


TABLE 3. Hazard Ratio Estimates for DCVS

	HR	95% CI	Z	P
UEAV: any vs none	1.6	[1.02, 2.62]	2.05	.041
Intervention: coiling vs clipping	0.5	[0.34, 0.77]	− 3.2	.001
Sex: female vs male	2	[1.26, 3.17]	2.92	.004
BNI scale (1-point increase)	1.9	[1.48, 2.48]	4.92	<.001
Intraparenchymal hemorrhage: yes vs no	0.5	[0.28, 0.89]	− 2.4	.019

grade and BNI scores in UEAV patients. Additionally, our UEAV patients presented in worse clinical condition and more often underwent insertion of an external ventricular drain. This finding reflects that of Baldwin et al., who reported an association

between hydrocephalus and UEAV.⁴ Poor initial neurological state has been identified as a clinical predictor of UEAV.^{3,4,8} In contrast, UEAV in asymptomatic patients seems to be uncommon and not associated with increased risk of DCI.²

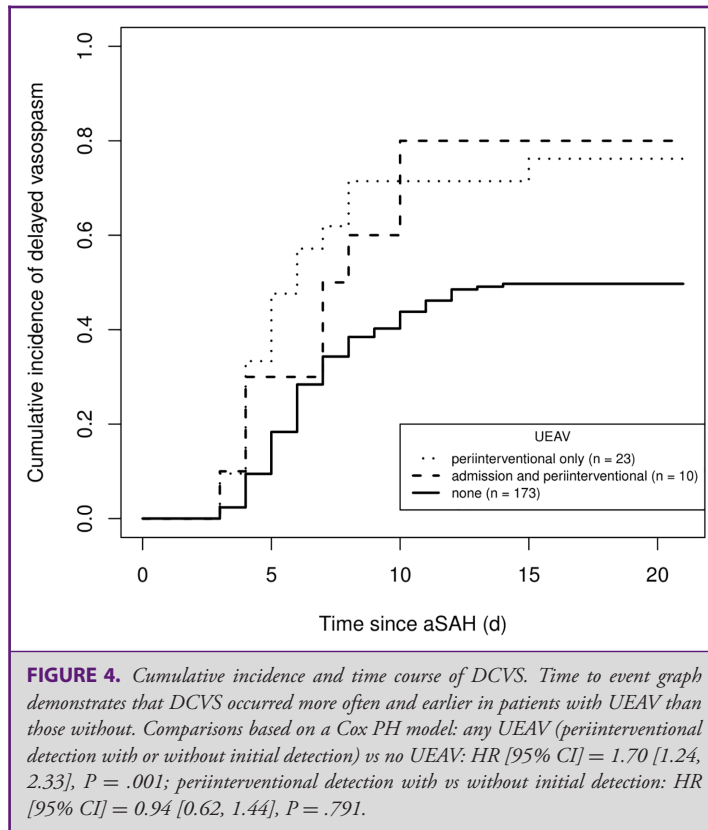


TABLE 4. Odds Ratio Estimates for DCI

	OR	95% CI	Z	P
UEAV: any vs none	5.9	[1.69, 25.09]	2.61	.009
Intervention: coiling vs clipping	0.3	[0.11, 0.52]	-3.5	<.001
Sex: female vs male	2.6	[1.19, 5.85]	2.35	.019
WFNS: poor vs good	3.9	[1.53, 10.79]	2.77	.006
BNI scale (1-point increase)	2.6	[1.80, 3.84]	4.93	<.001

TABLE 5. Odds Ratio Estimates for Poor Outcome

	OR	95% CI	Z	P
UEAV: any vs none	4.7	[1.66, 13.43]	2.9	.004
Age (1-yr increase)	1	[1.01, 1.08]	2.4	.017
WFNS: poor vs good	5	[2.04, 12.76]	3.5	<.001
Intraparenchymal hemorrhage: yes vs no	4.2	[1.67, 10.58]	3.1	.002

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Clinical Implications

In summary, these observations support the hypothesis that the main causes of UEAV are direct mechanical pressure or indirect arterial stretching (transferred via arachnoid bands) secondary to increased intracranial pressure, large subarachnoid blood clots, intraventricular hemorrhage, and hydrocephalus.^{3,4,22,32} This combination of findings suggests that any UEAV detected within the first 48 h after SAH has important clinical implications. An aggressive approach to reduce these mechanical factors (ie, early cerebrospinal fluid drainage and removal of intracerebral hematomas) could positively influence the further course of the disease. Based on findings in the literature and those in the presented study, we have changed our SAH treatment protocols. We have started to actively screen our patients for UEAV. In the presence of UEAV, we remove mechanical factors whenever possible and treat DCVS earlier and more aggressively.

UEAV has already been included in the BEHAVIOR score for the prediction of DCI in SAH patients.³³ On the basis of our findings and increasing evidence in the literature, this can also justify the inclusion of UEAV in vasospasm prediction scores. Future research should be undertaken to investigate whether active screening for UEAV and aggressive early therapy could attenuate DCVS, reduce DCI, and improve patient outcome in SAH patients.

CONCLUSION

Our findings suggest that patients with UEAV identified at admission or those with periinterventional UEAV are at high risk of DCVS, DCI, and poor outcome after SAH. Furthermore, our patients with UEAV developed DCVS, not only more often but earlier. Therefore, clinicians should interpret periinterventional UEAV as a warning sign, and adopt early close monitoring and consider that more aggressive therapy may be warranted in this population of SAH patients.

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Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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