Journal of Neuroradiology 46 (2019) 15–24

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Original article

Complication rate of intraarterial treatment of severe cerebral vasospasm after subarachnoid hemorrhage with nimodipine and percutaneous transluminal balloon angioplasty: Worth the risk?

Daniela Adami[a], Joachim Berkefeld[a], Johannes Platz[b], Jürgen Konczalla[b], Waltraud Pfeilschifter[c], Stefan Weidauer[d], Marlies Wagner[a,*]

[a] Institute of Neuroradiology, University Hospital Frankfurt, Goethe-University, Schleusenweg 2-16, 60528 Frankfurt, Germany
[b] Department of Neurosurgery, University Hospital Frankfurt, Goethe-University, Schleusenweg 2-16, 60528 Frankfurt, Germany
[c] Department of Neurology, University Hospital Frankfurt, Goethe-University, Schleusenweg 2-16, 60528 Frankfurt, Germany
[d] Neurology, Sankt Katharinen-Krankenhaus GmbH, Seckbacher Landstraße 65, 60389 Frankfurt, Germany

ARTICLE INFO

Article history:
Available online 4 May 2018

Keywords:
Subarachnoid hemorrhage
Cerebral vasospasm
Nimodipine
Complications

ABSTRACT

Background and purpose. – Delayed cerebral ischemia (DCI) is a complication of aneurysmal subarachnoid hemorrhage (SAH). Arterial cerebral vasospasm (CVS) is discussed as the main pathomechanism for DCI. Due to positive effects of per os nimodipine, intraarterial nimodipine application is used in patients with DCI. Further, percutaneous transluminal balloon angioplasty (PTA) is applied in focal high-grade spasm of intracranial arteries. However, clinical benefits of those techniques are unconfirmed in randomized trials so far, and complications might occur. We analyzed the occurrence of new infarcts in patients with severe CVS treated intra-arterially to assess benefits and risks of those techniques in a large single-center collective.

Materials and methods. – All imaging and clinical data of 88 patients with CVS after SAH and 188 procedures of intraarterial nimodipine infusion and additional PTA in selected cases (18 patients, 20 PTA procedures) treated at our institution were reviewed. In the event of new infarcts after endovascular treatment of CVS, infarct patterns were analyzed to determine the most probable etiology.

Results. – Fifty-three percent of patients developed new cerebral infarction after intraarterial nimodipine and additional PTA in selected cases. Hereunder 47% were caused by persisting CVS. In 6% of patients, 3% of procedures respectively, new infarcts occurred due to complications of the intraarterial treatment including thromboembolism and arterial dissection. Of those, 3% of patients, 2% of procedures respectively, were assigned to thrombembolic complications of digital substraction angiography for intraarterial nimodipine. 17% of all patients treated with PTA (3/18 = 17%) showed infarction as a complication of PTA (15% of all PTA procedures). In 1% of patients, etiology of new infarction remained unclear.

Conclusion. – Ischemic complications occur in about 6% of patients treated intraarterially for CVS, 3% of procedures respectively. Further, to date a benefit for patients treated with this therapy could not be proven. Therefore, intraarterial treatment of CVS should be performed only in carefully selected cases.

Introduction

Delayed cerebral ischemia (DCI) is a complication of subarachnoid hemorrhage (SAH) with significant impact on poor outcome [1,2]. After SAH, DCI appears 5 to 14 days after the initial bleeding in about 30%–46% of patients [3,4]. Clinical symptoms include focal neurological signs, decrease in level of consciousness, aphasia, and mutism [4,5]. The complete pathomechanism of DCI is not clear. Ecker and Riemenschneider detected arterial narrowing in patients after SAH in 1951 [6], and since then arterial cerebral vasospasm (CVS) has been suspected to play an essential role [7,8]. However, DCI can also occur without angiographic evidence of CVS [9,10], suggesting other factors also contributing to DCI [10–12]. Nevertheless, CVS is still assumed to be one main cause and moreover, this mechanistic theory provided mechanistic therapeutic approaches in the past [13,14].

* Corresponding author.
E-mail address: marlies.wagner@kgu.de (M. Wagner).

https://doi.org/10.1016/j.neurad.2018.04.001
0150-9861/

As a specific blocker of the L-Type voltage gated calcium channels, nimodipine constrains the contractile process of smooth muscle cells in cerebral vessels by blocking the influx of calcium, which results in the relaxation of constricted arteries. When administered orally, the L-type calcium channel blocker and vasodilator nimodipine has shown to be effective to prevent CVS in several randomized studies with a benefit on patient outcome [15,16].

Subsequently, intraarterial nimodipine application was routinely used with the aim to intensify the impact of nimodipine on the constricted vessel. However, the benefit of intraarterial nimodipine has never been proven in a randomized trial. Multiple studies reason that intraarterial nimodipine shows effective reduction of vasospastic vessels while being safe [17–19]. In experienced hands, endovascular nimodipine therapy is an uncomplicated intervention with low risk for complications. Nevertheless, other studies showed no impact on the long-term regression of CVS and clinical outcome of patients with DCI, and procedure-related complications were described [13,20,21]. Further, percutaneous transluminal angioplasty (PTA), an intravascular balloon catheter technique, has been performed in case of refractory CVS to dilate spastic arteries and restore cerebral blood flow. PTA has shown to treat focal CVS effectively [22,23], albeit its effect on clinical outcome has also not been proven in a randomized trial.

The therapeutic guidelines are inconsistent: selective intraarterial vasodilator therapy is recommended as a class IIa, level B therapy by the American Heart Association/American Stroke Association (AHA/ASA) [24], while the German Society of Neurology (DGN) proposes to use intravascular techniques only in selected cases after interdisciplinary consideration [25]. The inconsistence of the literature and guidelines as well as the urge of the treating physicians to prevent complications due to DCI – if at all possible – contribute to the differences in approach in different medical centers.

We therefore performed a retrospective single-center study on SAH-patients with CVS treated with intraarterial nimodipine and/or balloon angioplasty to evaluate the effect and risks of those techniques with the aim to contribute to a larger basis for decision-making.

Table 1
Degree of CVS.

Degree of CVS	Reduction of arterial diameter compared to admission
None/Mild	0–33%%
Moderate	34–66%
Severe	≥ 67%

Materials and methods

The Institutional Review Board has approved this retrospective study.

Eighty-eight patients with angiographic CVS and intraarterial application of nimodipine were included in the study. Additional PTA was applied only in selected cases.

Further inclusion criteria were: age between 18 and 100 years, proven SAH on computed tomography (CT) or magnetic resonance imaging (MRI), detection of CVS using CT- or MR-angiography (CTA/MRA) or digital substraction angiography (DSA) [26]. Patients with non-aneurysmal SAH were excluded from the study.

CT was performed in each patient on admission and 24 h after aneurysm treatment (in selected cases, for example in very young patients, MRI was performed instead of CT). After treatment of the aneurysms, all patients received nimodipine from the day of admission either orally (6 × 60 mg/day) or intravenously (2 mg/h). Routine monitoring included daily transcranial Doppler (TCD) measurements. If DCI was suspected because of new neurological deficits or accelerated blood flow velocities on ultrasound Doppler sonography, immediately follow-up CT or MRI was performed. In case of new infarcts on follow-up CT or MRI or disturbance of perfusion parameters on CT and MR perfusion measurement [27,28], e.g. prolonged mean transit time (MTT), additional biplane DSA was obtained to analyze extent of CVS. Extend of CVS was defined on a widely used classification using the reduction of arterial diameter compared to DSA on admission (Table 1). Mean arterial pressure of patients with severe CVS was adjusted to 100 mmHg (in the absence of contraindications). Intraarterial nimodipine application and additional PTA in selected cases was initiated in case of severe vascular narrowing (≥ 67%).

Table 2
Patient collective.

	Pat w infarcts	Pat w/o infarcts	*P*-value	Total
No. of patients	47 (53%) 42 due do CVS (48%) 5 due to complications (6%)	41 (46.59%)		88 (100%)
Procedures in total 188	5/188 (3%)			
Average Number of Nimodipin treatments per patient (SD)	2,36(±1,26)	2,07(±1,01)	0.24	2,22(±1,14)
Average age (SD)	51.1 (± 10.62)	48 (± 11)	0.18	49.6 (± 10.8)
Gender (m:f)	16:31	9:32		25:63
Average of Hunt and Hess Grade (SD)	3.04(± 1.18)	3.0(± 1.09)	0.87	3.02(± 1.13)
I	4 (1)	2		6 (6.82%)
II	13	13		26 (29.55%)
III	13 (1)	14		27 (30.68%)
IV	11 (2)	7		18 (20.45%)
V	6 (1)	5		11 (12.5%)
3-months mRS	3.15 ± 2.02	2.14 ± 1.68	0.01	66
Location of Aneurysm				
Internal carotid artery	6	8		14 (15.9%)
Anterior cerebral artery	25 (2)	17		42 (47.73%)
Middle cerebral artery	12 (1)	6		18 (20.45%)
Posterior circulation	7 (2)	12		19 (21.59%)
Multiple aneurysms	4	1		5 (5.68%)
Treatment of aneurysm				
Clipping	20	15		35
Coiling	23	24		47
Combination	1	0		1
Unknown source of bleeding	3	2		5

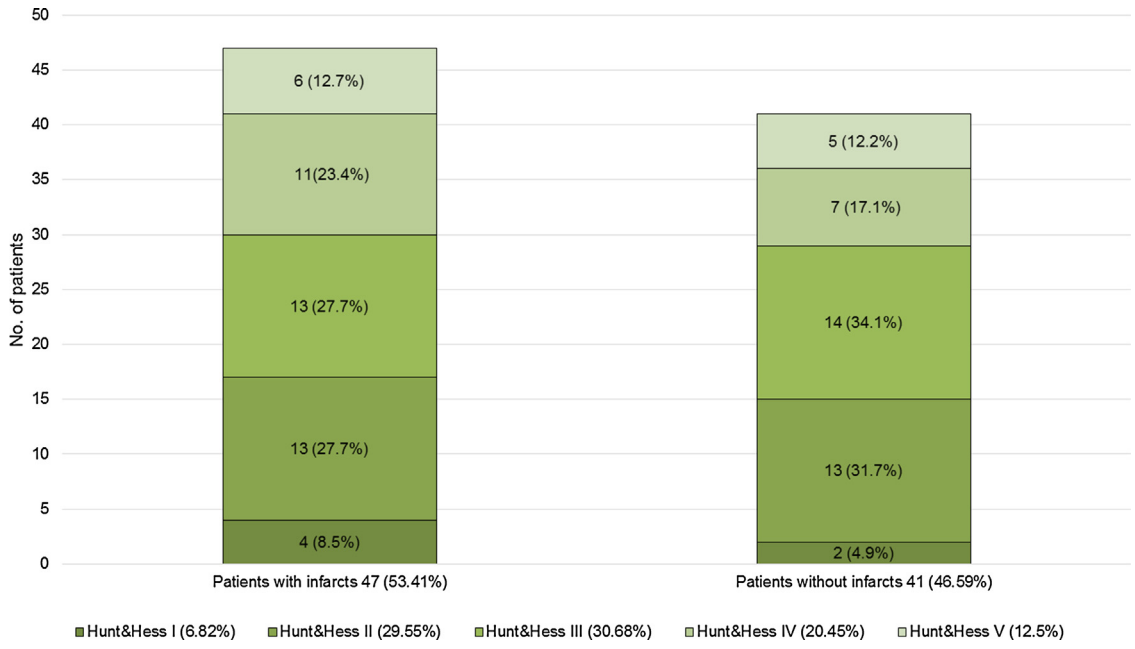

Fig. 1. Hunt and Hess Grade.

All patients were treated in anesthetic stand-by to prevent low blood pressure during nimodipine application. In case of intraarterial treatment, 5000 IE heparin were given intravenously. Afterwards, a 5F diagnostic catheter was placed in the proximal internal carotid artery or the proximal vertebral artery. Nimodipine was applied selectively intraarterial with a bolus of 0.8 mg nimodipine soluted in 10 mL NaCl given first over five to ten minutes followed by a pump-infusion of 4 mg nimodipine in a 50 mL NaCl solution over 30 min. In case of persisting severe circumscribed CVS cautious PTA (below vessel diameter) was performed after replacing the diagnostic catheter by a 5F- or 6F-guiding catheter.

Afterwards, clinically indicated follow up CT or MRI were analyzed and compared to preinterventional CT or MRI. For new infarcts after endovascular treatment of CVS, infarct patterns were consensually analyzed by three experienced neuroradiological reviewers using all clinical and radiological data to determine the most probable etiology.

Newly developed infarctions were classified using the following patterns:

- infarction due to cerebral CVS;
- infarction as a complication of endovascular treatment of CVS;
- infarction of unknown origin.

Results

A total of 88 (62 female, 79%) patients were included in the analysis (Table 2).

Age ranged from 27 to 74 years (mean 49.6 years). Hunt and Hess grade ranged from one to five (mean 3.02) (Fig. 1). Average Hunt and Hess grade did not differ between patients with and patients without DCI (3.04 vs. 3.0). The grade of CVS ranged from moderate to highest grade in both groups (Table 1, Fig. 2). The type of aneurysmal treatment (clipping/coiling) did not have significant influence on the infarction rate (Table 2).

All patients (100%) received intraarterial nimodipine treatment. Additional PTA was performed in 18/88 (20.5%) patients in case of refractory CVS and persistent circumscribed high-grade vessel constriction (Table 1).

Three months modified ranking scale (mRS) clinical outcome data [29] could be obtained in 66 patients, 35 from the group of patients without new infarction, 33 from the group with new infarction. Patients with new infarcts showed a significantly worse 3-months mRS of 3.15 ± 2.02 compared to patients without new infarcts showing a 3-months mRS of 2.14 ± 1.68 ($P = 0.01$) (Table 2).

Patients with nimodipine

Of 88 CVS patients treated intraarterially with nimodipine in 188 procedures, 41/88 (47%) did not show new infarcts. Of the 47/88 (53%) patients with new infarcts after i.a. treatment, 42/47 (89%, 42/88 [89%]) were due to persisting or recurring CVS. 5/47 (6%, 5/88 [11%]) of patients and 5/188 (3%) of all procedures showed new infarction related to complications of intraarterial treatment. Of those, infarction in two patients (2/47 [4%], 2/88 [2%]) and 2/188 (1%) of all procedures were caused by DSA-related thromboembolic events. In three of the 18 patients (17%) treated with additional PTA in 20 procedures (15%), infarcts were caused by PTA-related events.

The immediate short time effect, which was described angiographically by increase of arterial diameter, ranged from restored normal diameter to no response. After application of nimodipine, 52 (59%) patients showed good immediate response to nimodipine (improvement of at least two grades of CVS (Table 1) or normalization of arterial diameter), whereas 30 (34%) had moderate (increase of arterial diameter of at least one grade (Table 1)), and six (7%) had poor or no response to treatment. There was no significant difference ($P = 0.89$) regarding response to nimodipine between the patients with new infarcts and those without (Fig. 3).

Of the 88, 47 (53%) patients developed new cerebral infarction after intraarterial treatment detected by follow up CT or MRI (Fig. 4). Forty-two of those patients (42/88 = 48%, 42/47 = 89%) showed infarct patterns compatible with CVS (Figs. 4 and 5).

Patients with additional PTA

In 18/88 (20.45%) patients, 20 PTAs were performed in case of insufficient nimodipine-effect and persistent circumscribed

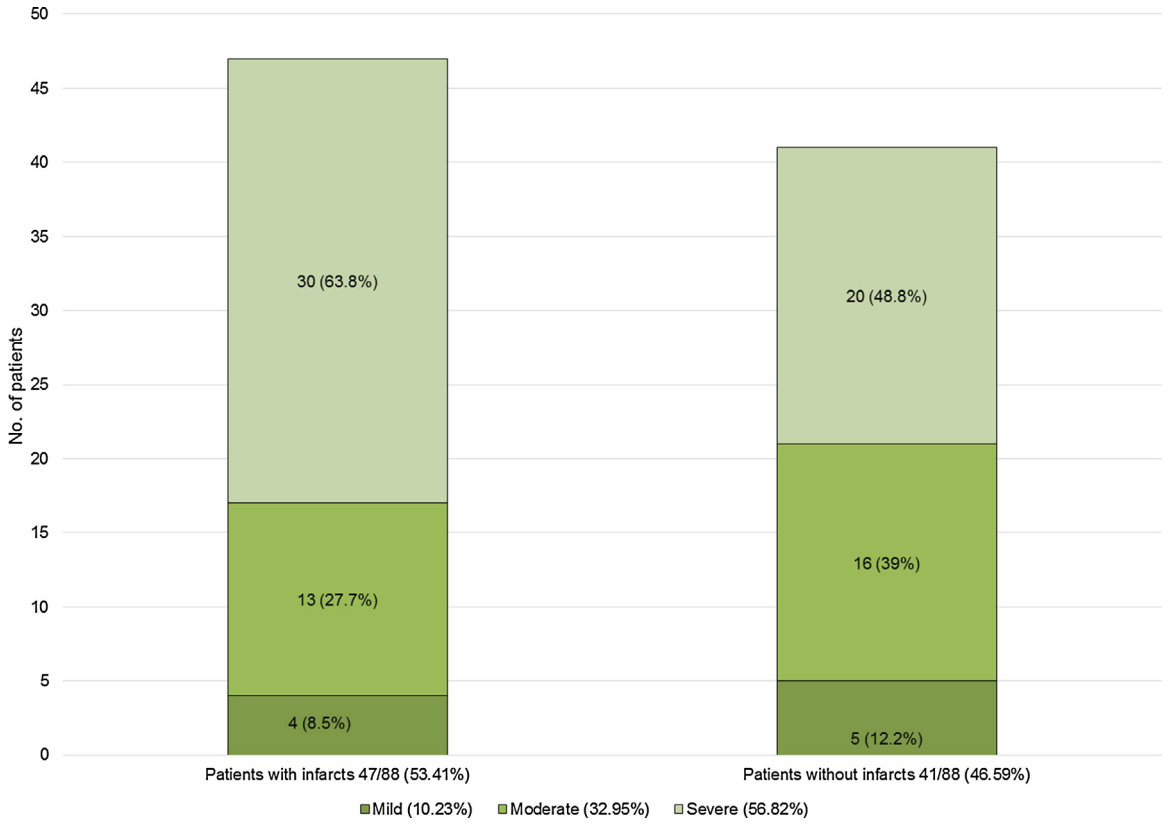

Fig. 2. Severity of CVS.

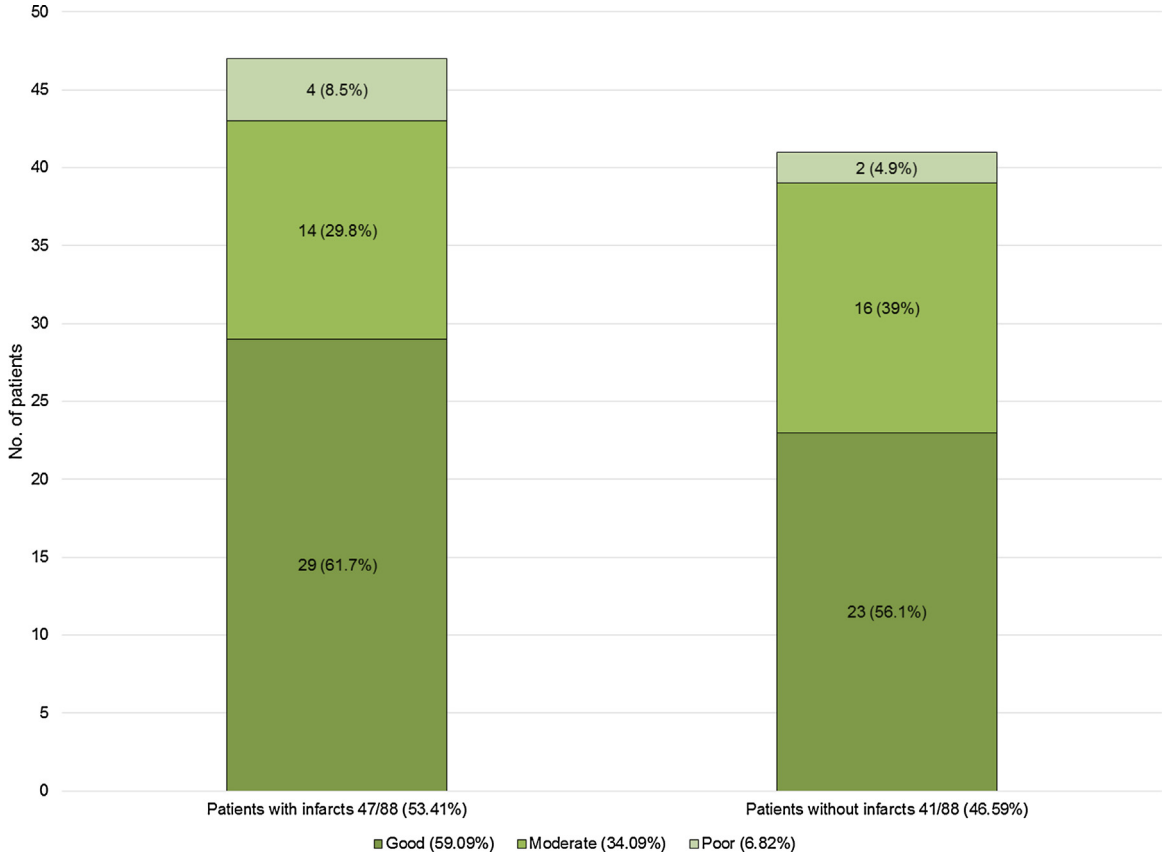

Fig. 3. Increase of arterial diameter after application of intraarterial nimodipine.

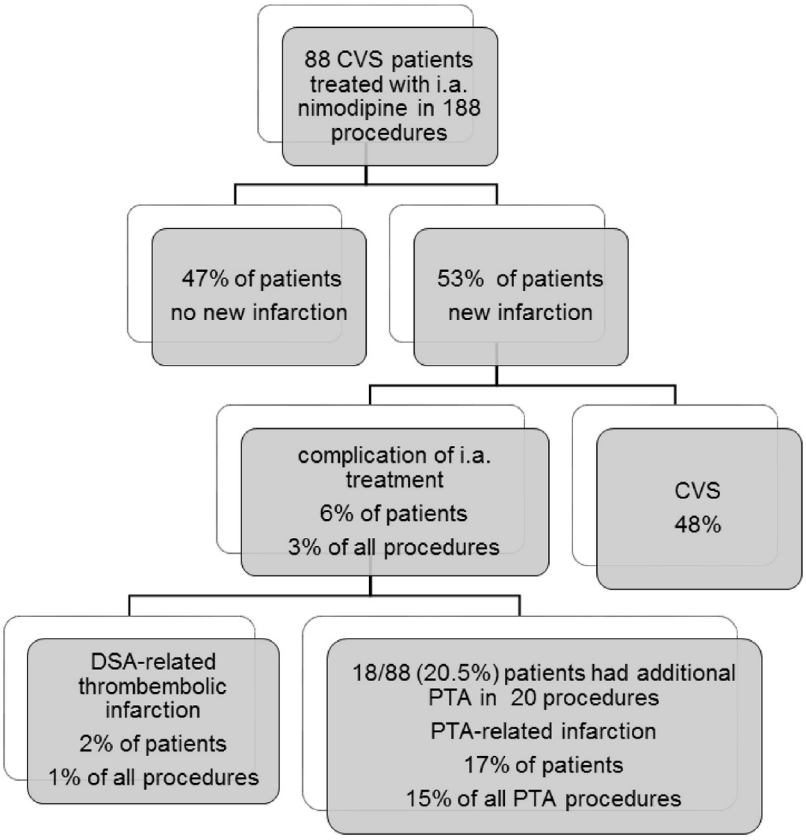

Fig. 4. Flow chart of complications.

high-grade vessel constriction. Of those, 11/18 patients (61%) showed good response to PTA with distinct increase of arterial diameter and arterial blood flow. In 6/18 (33%) patients there was moderate response to PTA, and 1/18 (5.5%) patient did not show positive response (procedure-related arterial dissection) (Fig. 6). Of 18 patients with additional PTA treatment, 12/18 (67%) patients developed new infarction (Fig. 6). Of those, 9/12 (75%) were compatible with CVS, and 3/12 (25%) were caused by complications of PTA resulting in 15% of all PTA procedures (Table 3).

In total, 5/88 patients (6%) with 188 procedures (5/188, 3%) (Fig. 4) developed 7 infarcts with patterns other than CVS-associated:

- two patients treated with intraarterial nimodipine showed cuneiform territorial infarcts (Fig. 7AB), and one patient showed dot-like infarcts (Fig. 7C–D) outside the territory of the spastic arteries, but within the territory of an angiographically depicted artery compatible with thromboembolic complications of DSA;
- two patients developed infarction after PTA in the vascular territory of the dilated artery compatible with embolic complications of PTA;
- in one patient, one infarct occurred in the territory of an iatrogenic dissected artery after PTA;
- in one patient, no clear etiology could be determined for new infarcts. Those infarcts occurred in the territory of the right superior cerebellar artery ten days after endovascular treatment of a basilar tip aneurysm with coiling. On day six and day ten, endovascular treatment of CVS was performed with nimodipine and PTA in both internal carotid arteries but not in the posterior circulation.

Discussion

The use of intraarterial nimodipine and/or balloon angioplasty to prevent DCI in patients with severe CVS after SAH is still controversial and to date, a clinical benefit could not be proven in a randomized clinical trial [24,25]. Besides, although those endovascular procedures are standardized and easy to perform for trained neurointerventionalists, procedure-related complications cannot be avoided completely. On the other hand, however, recurrent treatment success in selected cases and lack of alternatives lead to maintenance of these treatment options in many centers.

In our single-center patient collective of 88 SAH patients with severe CVS treated intraarterially 188 times with nimodipine and additional PTA in selected cases, we found 53% patients to develop new ischemic lesions, while 47% did not show any signs of cerebral infarction (Table 2). In patients with new infarcts after endovascular treatment of CVS, 89% (42/47 = 89.4%) were most probably caused by recurrent CVS, while 11% (5/47 = 10.6%) of patients resulting in 3% of all procedures were caused by procedure-related complications (Table 2). Of all patients treated intraarterially (88 patients in total), this represents CVS-related infarcts in 47% (41/88), and infarcts because of procedure-related complications in nearly 6% (5/88) of patients (3% of all procedures). This is in line with other studies, where CVS-related infarctions after intraarterial treatment with nimodipine are reported in 21–62% of patients [13]. However, there are very few studies in the literature reporting rates of infarction in SAH patients with CVS but without intraarterial treatment of CVS: Weidauer et al. [30] reported CVS associated infarcts in 52.5% of patients. If one compares those patients not treated intraarterially developing infarction in 52.5% of cases to our collective of patients treated intraarterially developing new

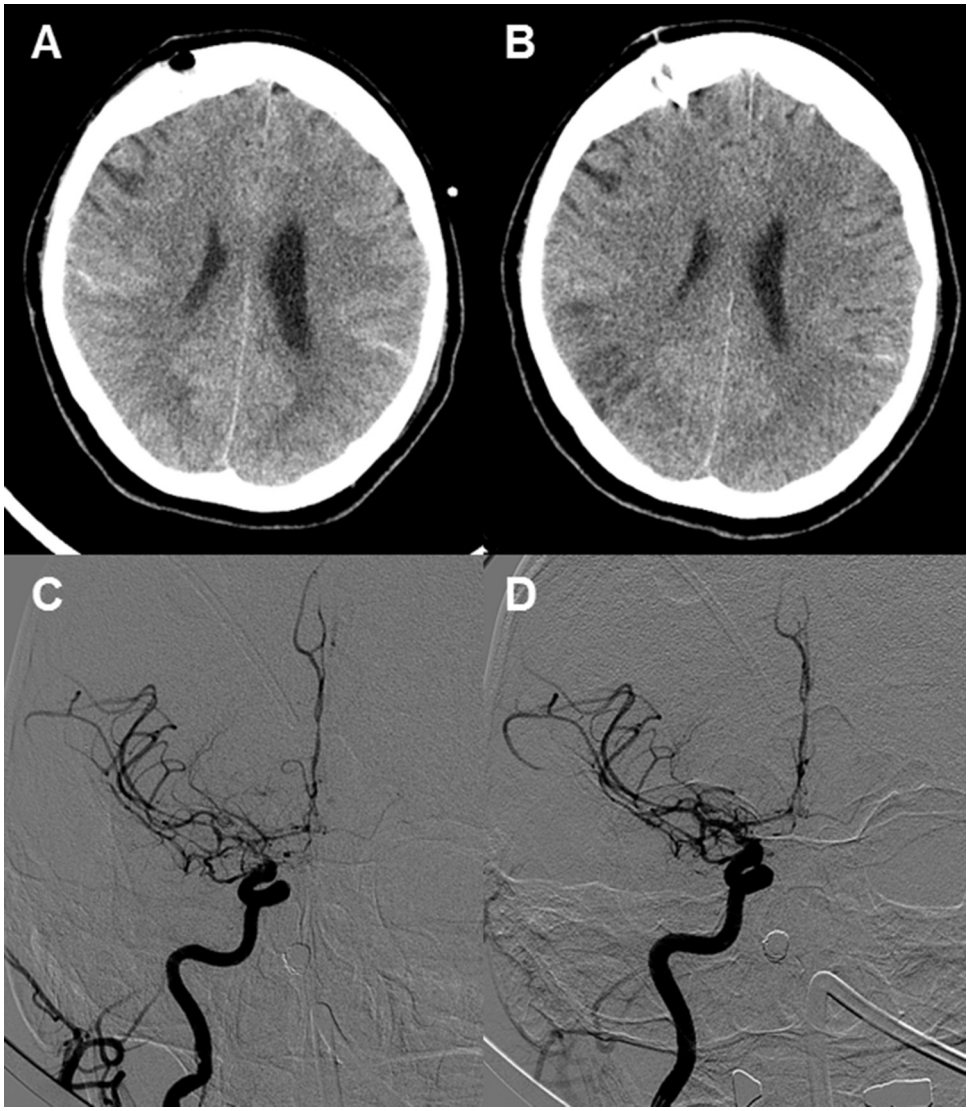

Fig. 5. CT (A, B) and DSA (C, D) show new infarcts in the posterior right MCA territory before (A, C) and after technical successful endovascular treatment of the right ACI (B) with nimodipine and PTA of the right M1 segment and the right terminal ACI segment (D).

infarcts in 53% of cases, those results could lead to the interpretation that SAH patients with CVS treated intraarterially do not benefit from intraarterial treatment. Therefore, intraarterial CVS treatment should be recommended as routine therapy in CVS patients, but should not be limited to selected patients only.

One might assume that in the group of patients without infarction the degree of CVS might have been lower, or that response to nimodipine might have been better. However, there was no difference between both groups regarding both aspects ($P = 0.68$ for the degree of CVS, $P = 0.89$ for degree of response to nimodipine) (Fig. 3).

In the group of patients with new infarcts related to CVS after intraarterial nimodipine, 61.7% (29/47) of patients had shown a good immediate response to nimodipine with a distinct increase of the arterial diameter and restored perfusion (Fig. 3). Although some authors report the opposite, the development of recurrent CVS after intraarterial nimodipine is well known and probably due to a rebound effect [31]. One might assume that continuous intraarterial application of nimodipine might prevent the rebound effect and the development of recurrent CVS, and Muhsal et al. [32] reported about good response to continuous intraarterial nimodipine-application without new ischemic lesions after treatment. However, other authors described new infarctions even after continuous intraarterial nimodipine application [14].

On the other hand, 48.8% of our patients with severe CVS remained without new ischemic lesions (Fig. 2). Those findings support the theory that hemodynamic effects of delayed CVS and vascular narrowing as the only cause of infarction might be overestimated, and that in fact there are multifactorial processes leading to DCI [10] (see below).

Not surprisingly, patients without new infarcts showed a significantly better 3-months mRS compared to patients developing new infarcts ($P = 0.01$) [29].

In our study, seven new cerebral infarctions were caused by intraarterial treatment of CVS in 5/88 patients (6%), 3% of all procedures respectively.

In three of the patients (3%), 2% of all procedures respectively, thromboembolic complications occurred during DSA (6 A-D). This is in line with the literature, where thromboembolic complications after application of intraarterial nimodipine are reported in 3% [33]

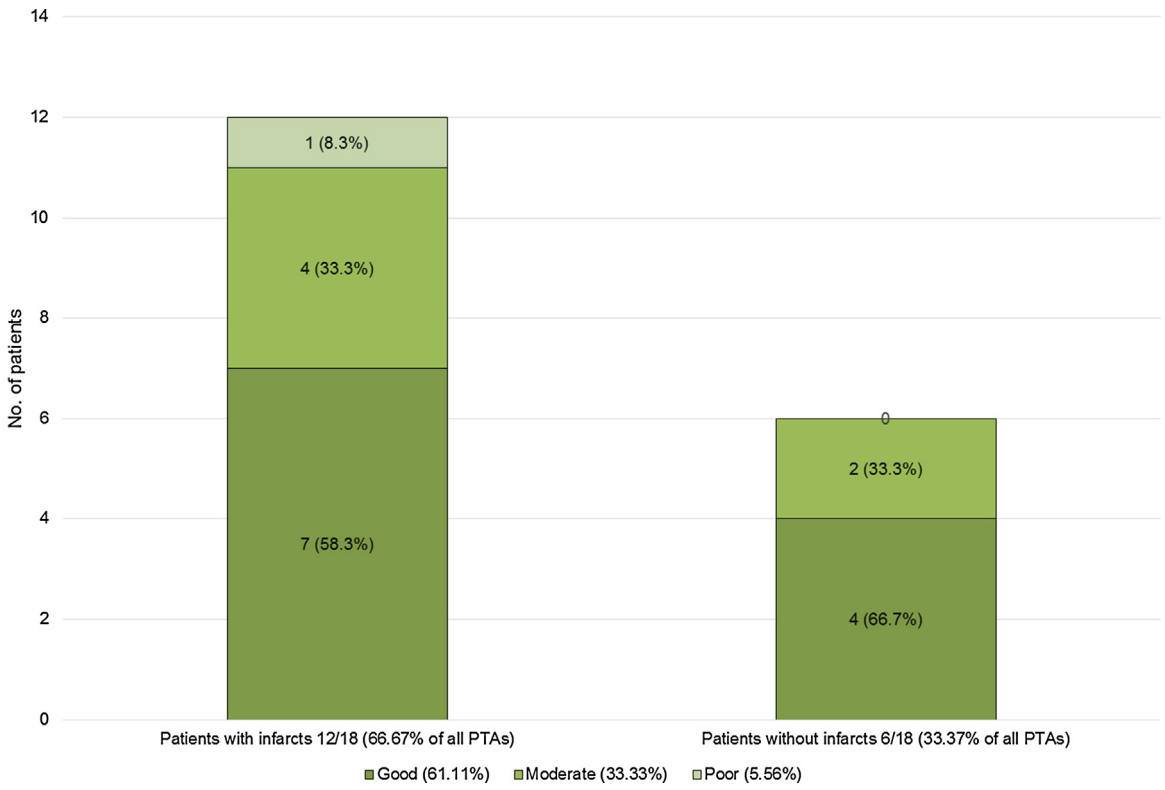

Fig. 6. Increase of arterial diameter after PTA.

to 10% [20]. In contrast to diagnostic DSA with complication rates of less than 1.3% [34,35], the higher number of thromboembolic complications in SAH patients with CVS might be mainly explained by two aspects:

- in SAH, coagulation and inflammatory systems are activated [36], which increases the risk of thromboembolism;
- catheters are left in the artery for up to half an hour, which further increases the risk of thromboembolism even after intravenous application of heparin. However, it must be emphasized that in our collective none of those thromboembolic infarcts was attributed directly to intraarterial nimodipine infusion because all those infarcts occurred outside the treated arterial territory.

PTA has been proven to be a procedure with low risk for complications [37–39] even in vasospastic arteries [40,41]. However, complications include increasing CVS, arterial dissection and vessel rupture [42].

In our study, we found 17% of all patients treated with PTA, 15% of all PTA procedures respectively, to show infarction as a complication of PTA. While two patients (2/18 = 11% of all performed PTAs) showed infarct patterns compatible to thromboembolic complications of PTA, one patient suffered from arterial dissection, which resulted in territorial infarction. It has to be stated that only few highly selected, worst affected patients in our institution were treated with PTA in case of most severe CVS as ultima ratio when all other treatment options had failed. This might explain why our collective is comparatively low and complications are higher compared to other studies focusing on PTA in CVS patients (Table 3). In patients with CVS, the increased resistance of the vessel wall muscles requires a higher inflation pressure for vessel expansion [43] increasing the risk for arterial dissection. In the presented study however, dissection did not occur during balloon inflation but while bringing the balloon catheter up. Further, risk of thromboembolism is increased in patients with SAH due to activated coagulation cascades, and after PTA, endothelial damage and disruption of the collagen fibers in vessel walls [44] might also increase the risk of thrombus formation.

Table 3
Complications of PTA reported in our collective in relation to studies in the literature.

Studies reporting on complications of PTA	Complication rate
Our collective	15% (3/20 procedures)17% (3/18 patients)
Bejjani GK et al. [36]	4% (3/81 procedures) 14% (3/21 patients)
Chaudhry NS et al. [58]	0% (82 procedures, 17 patients)
Patel AS et al. [59]	0% (165 procedures, 42 patients)
Terry A et al. [60]	5% (4/85 procedures) 7% (4/57 patients)
Choi BJ et al. [61]	0% (54 procedures, 11 patients)

In our study, one patient showed embolic cerebellar infarction of unknown etiology. It cannot be ruled out that DSA-related thromboembolism caused the cerebellar infarcts. Further, there are several additional hypotheses for infarcts in patients with SAH apart from CVS including dysfunction of the cerebral autoregulation [45,46]; metabolic changes [47], abnormal immune response [48,49], activation of the inflammatory cascade with elevated levels of cytokines and eicosanoid reaction [50,51], abnormal release of vasodilators like nitrogen monoxide [52,53], disturbance of the microcirculation [17,32], activation of the coagulation system [54,55], and spreading depolarization [12,56,57].

Limitation

As a limitation, it has to be clearly noted that the results of our retrospective study are focused on imaging results. It would have needed a prospective design to allow referring valuable clinical outcome data on application of intraarterial CVS treatment.

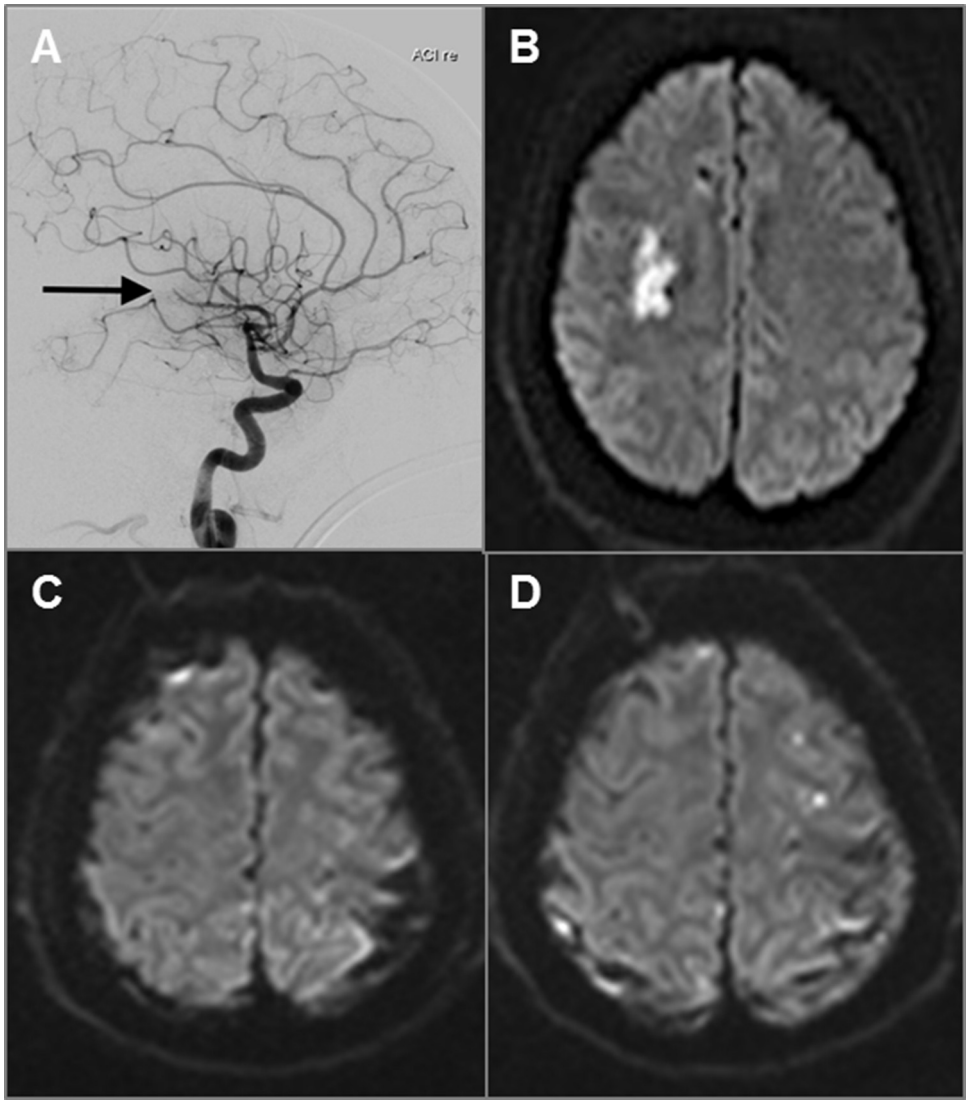

Fig. 7. Thromboembolic complications after DSA for intraarterial nimodipine application (outside the treated territory): Thromboembolism in the right middle cerebral artery shown on DSA (A) with consecutive infarction shown on MRI with DWI (B). MRI (DWI) shows new thromboembolic infarcts in the territory of the left middle cerebral artery before DSA (C) and after DSA (D).

Conclusion

Because more than 50% of treated patients developed new infarcts, our study could not prove a convincing benefit for patients with SAH and severe CVS treated with intraarterial nimodipine and additional PTA in selected cases regarding the development of new infarcts. Besides, the risk of procedure-related ischemic complications is 3%, affecting nearly 6% of patients. While there was no infarct as a direct complication of intraarterial nimodipine infusion, an increased risk of periprocedural thromboembolic complication is presumed. In contrast, the risk of thromboembolic complication or arterial dissection of PTA in patients with CVS after SAH is relatively high (17%, 15% of all PTA procedures respectively). Therefore, intraarterial treatment of CVS, especially PTA, should not be recommended as a standard procedure in patients even with severe CVS, but should be considered only in selected cases as last treatment option and rescue therapy.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Roos YB, de Haan RJ, Beenen LF, Groen RJ, Albrecht KW, Vermeulen M. Complications and outcome in patients with aneurysmal subarachnoid haemorrhage: a prospective hospital based cohort study in the Netherlands. J Neurol Neurosurg Psychiatry 2000;68:337–41.
[2] Solenski NJ, Haley Jr EC, Kassell NF, Kongable G, Germanson T, Truskowski L, et al. Medical complications of aneurysmal subarachnoid hemorrhage: a report of the multicenter, cooperative aneurysm study. Participants of the Multicenter Cooperative Aneurysm Study. Crit Care Med 1995;23:1007–17.
[3] Fergusen S, Macdonald RL. Predictors of cerebral infarction in patients with aneurysmal subarachnoid hemorrhage. Neurosurgery 2007;60: 658–67.
[4] Hijdra A, Van Gijn J, Stefanko S, Van Dongen KJ, Vermeulen M, Van Crevel H. Delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: clinicoanatomic correlations. Neurology 1986;36:329–33.
[5] Fisher CM, Roberson GH, Ojemann RG. Cerebral vasospasm with ruptured saccular aneurysm – the clinical manifestations. Neurosurgery 1977;1:245–8.
[6] Ecker A, Riemenschneider PA. Arteriographic demonstration of spasm of the intracranial arteries, with special reference to saccular arterial aneurysms. J Neurosurgery 1951;8:660–7.
[7] Crowley RW, Medel R, Dumont AS, Ilodigwe D, Kassell NF, Mayer SA, et al. Angiographic vasospasm is strongly correlated with cerebral infarction after subarachnoid hemorrhage. Stroke 2011;42:919–23.
[8] Vajkoczy P, Horn P, Thome C, Munch E, Schmiedek P. Regional cerebral blood flow monitoring in the diagnosis of delayed ischemia following aneurysmal subarachnoid hemorrhage. J Neurosurg 2003;98:1227–34.

[9] Dhar R, Scalfani MT, Blackburn S, Zazulia AR, Videen T, Diringer M. Relationship between angiographic vasospasm and regional hypoperfusion in aneurysmal subarachnoid hemorrhage. Stroke 2012;43:1788–94.
[10] Wagner M, Steinbeis P, Güresir E, Hattingen E, du Mesnil de Rochemont R, Weidauer S, et al. Beyond delayed cerebral vasospasm: infarct patterns in patients with subarachnoid hemorrhage. Clin Neuroradiol 2013;23: 87–95.
[11] Vergouwen MDI, Ilodigwe D, Macdonald RL. Cerebral infarction after subarachnoid hemorrhage contributes to poor outcome by vasospasm-dependent and -independent effects. Stroke 2011;42:924–9.
[12] Woitzik J, Dreier JP, Hecht N, Fiss I, Sandow N, Major S, et al. Delayed cerebral ischemia and spreading depolarization in absence of angiographic vasospasm after subarachnoid hemorrhage. J Cereb Blood Flow Metab 2012;32: 203–12.
[13] Hänggi D, Turowski B, Beseoglu K, Yong M, Steiger HJ. Intra-arterial nimodipine for severe cerebral vasospasm after aneurysmal subarachnoid hemorrhage: influence on clinical course and cerebral perfusion. AJNR Am J Neuroradiol 2008;29:1053–60.
[14] Ott S, Jedlicka S, Wolf S, Peter M, Pudenz C, Merker P, et al. Continuous selective intra-arterial application of nimodipine in refractory cerebral vasospasm due to aneurysmal subarachnoid hemorrhage. BioMed Res Int 2014:970741.
[15] Barker FG, Ogilvy CS. Efficacy of prophylactic nimodipine for delayed ischemic deficit after subarachnoid hemorrhage: a metaanalysis. J Neurosurg 1996;84:405–14.
[16] Ohman J, Servo A, Heiskanen O. Long-term effects of nimodipine on cerebral infarcts and outcome after aneurysmal subarachnoid hemorrhage and surgery. J Neurosurg 1991;74:8–13.
[17] Firat MM, Gelebek V, Orer HS, Belen D, Firat AK, Balkanci F. Selective Intraarterial Nimodipine Treatment in an Experimental Subarachnoid Hemorrhage Model. AJNR Am J Neuroradiol 2005;26:1357–62.
[18] Hui C, Lau KP. Efficacy of intra-arterial nimodipine in the treatment of cerebral vasospasm complicating subarachnoid haemorrhage. Clin Radiol 2005;60:1030–6.
[19] Oran I, Cinar C. Continuous intra-arterial infusion of nimodipine during embolization of cerebral aneurysms associated with vasospasm. AJNR Am J Neuroradiol 2008;29:291–5.
[20] Dehdashti AR, Binaghi S, Uske A, Regli L. Intraarterial nimodipine for the treatment of symptomatic vasospasm after aneurysmal subarachnoid hemorrhage: a preliminary study. Neurol India 2011;59:810–6.
[21] Ryu C-W, Koh J-S, Yu S-Y, Kim EJ. Vasogenic edema of the Basal Ganglia after intra-arterial administration of nimodipine for treatment of vasospasm. J Korean Neurosurg Soc 2011;49:112–5.
[22] Rosenwasser RH, Armonda RA, Thomas JE, Benitez RP, Gannon PM, Harrop J. Therapeutic modalities for the management of cerebral vasospasm: timing of endovascular options. Neurosurgery 1999;44:975–9.
[23] Zubkov YN, Nikiforov BM, Shustin VA. Balloon catheter technique for dilatation of constricted cerebral arteries after aneurysmal SAH. Acta Neurochir (Wien) 1984;70:65–79 [4].
[24] Connolly Jr ES, Rabinstein AA, Carhuapoma JR, Derdeyn CP, Dion J, Higashida RT, et al. American Heart Association Stroke Council; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; Council on Cardiovascular Surgery and Anesthesia; Council on Clinical Cardiology. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professionals from the American Heart Association/american Stroke Association. Stroke 2012;43:1711–37.
[25] Deutsche Gesellschaft für Neurologie: leitlinien für Diagnostik und Therapie in der Neurologie. Subarachnoidalblutung; 2012.
[26] Saba L, di Martino M, Siotto P, Anzidei M, Argiolas GM, Porcu M, et al. Radiation dose and image quality of computed tomography of the supra-aortic arteries: a comparison between single-source and dual-source CT scanners. J Neuroradiol 2018;45:136–41.
[27] Rubbert C, Caspers J, Petridis AK, Turowski B, May R. Dynamics of cerebral perfusion deficits after aneurysmal SAH - predictive value of early MTT for subsequent MTT deterioration. J Neuroradiol 2017;44:371–6.
[28] Labriffe M, Ter Minassian A, Pasco-Papon A, N'Guyen S, Aubé C. Feasibility and validity of monitoring subarachnoid hemorrhage by a noninvasive MRI imaging perfusion technique: Pulsed Arterial Spin Labeling (PASL). J Neuroradiol 2015;42:358–67.
[29] Zidan M, Gawlitza M, Metaxas G, Foussier C, Soize S, Pierot L. Endovascular treatment of intracranial aneurysms with Barricade coils: feasibility, procedural safety, and immediate postoperative anatomical results. J Neuroradiol 2016;43:353–7.
[30] Weidauer S, Lanfermann H, Raabe A, Zanella F, Seifert V, Beck J. Impairment of cerebral perfusion and infarct patterns attributable to vasospasm after aneurysmal subarachnoid hemorrhage: a prospective MRI and DSA study. Stroke 2007;38:1831–6.
[31] Biondi A, Ricciardi GK, Puybasset L, Abdennour L, Longo M, Chiras J, et al. Intra-arterial nimodipine for the treatment of symptomatic cerebral vasospasm after aneurysmal subarachnoid hemorrhage: preliminary results. AJNR Am J Neuroradiol 2004;25:1067–76.
[32] Musahl C, Henkes H, Vajda Z, Coburger J, Hopf N. Continuous local intra-arterial nimodipine administration in severe symptomatic vasospasm after subarachnoid hemorrhage. Neurosurgery 2011;68:1541–7.
[33] Cho WS, Kang HS, Kim JE, Kwon OK, Oh CW, Son YJ, et al. Intra-arterial nimodipine infusion for cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage. Interv Neuroradiol 2011;17:169–78.
[34] Kaufmann TJ, Huston J, Mandrekar JN, Schleck CD, Thielen KR, Kallmes DF. Complications of diagnostic cerebral angiography: evaluation of 19,826 consecutive patients. Radiology 2007;243:812–9.
[35] Willinsky RA, Taylor SM, TerBrugge K, Farb RI, Tomlinson G, Montanera W. Neurologic complications of cerebral angiography: prospective analysis of 2,899 procedures and review of the literature. Radiology 2003;227: 522–8.
[36] Kasuya H, Shimizu T, Okada T, Takahashi K, Summerville T, Kitamura K. Activation of the coagulation system in the subarachnoid space after subarachnoid haemorrhage: serial measurement of fibrinopeptide A and bradykinin of cerebrospinal fluid and plasma in patients with subarachnoid haemorrhage. Acta Neurochir (Wien) 1988;91:120–5.
[37] Bejjani GK, Bank WO, Olan WJ, Sekhar LN. The efficacy and safety of angioplasty for cerebral vasospasm after subarachnoid hemorrhage. Neurosurgery 1998;42:979–86.
[38] Chalouhi N, Tjoumakaris S, Thakkar V, Theofanis T, Hammer C, Hasan D, et al. Endovascular management of cerebral vasospasm following aneurysm rupture: outcomes and predictors in 116 patients. Clin Neurol Neurosurg 2014;118:26–31.
[39] Gifford E, Drazin D, Dalfino JC, Nair AK, Yamamoto J, Boulos AS. The effectiveness of microballoon angioplasty in treating middle cerebral artery occlusion beyond the bifurcation. AJNR Am J Neuroradiol 2010;31:1541–8.
[40] Coyne TJ, Montanera WJ, Macdonald RL, Wallace MC. Percutaneous transluminal angioplasty for cerebral vasospasm after subarachnoid hemorrhage. Can J Surg 1994;37:391–6.
[41] Murai Y, Kominami S, Kobayashi S, Mizunari T, Teramoto A. The long-term effects of transluminal balloon angioplasty for vasospasms after subarachnoid hemorrhage: analyses of cerebral blood flow and reactivity. Surg Neurol 2005;64:122–6.
[42] Rabinstein AA, Friedman JA, Weigand SD, McClelland RL, Fulgham JR, Manno EM, et al. Predictors of cerebral infarction in aneurysmal subarachnoid hemorrhage. Stroke 2004;35:1862–6.
[43] Honma Y, Fujiwara T, Irie K, Ohkawa M, Nagao S. Morphological changes in human cerebral arteries after percutaneous transluminal angioplasty for vasospasm caused by subarachnoid hemorrhage. Neurosurgery 1995;36:1073–80.
[44] Yamamoto Y, Smith RR, Bernanke DH. Mechanism of action of balloon angioplasty in cerebral vasospasm. Neurosurgery 1992;30:1–5.
[45] Hattingen E, Blasel S, Dettmann E, Vatter H, Pilatus U, Seifert V, et al. Perfusion-weighted MRI to evaluate cerebral autoregulation in aneurysmal subarachnoid haemorrhage. Neuroradiology 2008;50:929–38.
[46] Lang EW, Diehl RR, Mehdorn HM. Cerebral autoregulation testing after aneurysmal subarachnoid hemorrhage: the phase relationship between arterial blood pressure and cerebral blood flow velocity. Crit Care Med 2001;29: 158–63.
[47] Wagner M, Jurcoane A, Hildebrand C, Güresir E, Vatter H, Zanella FE, et al. Metabolic changes in patients with aneurysmal subarachnoid hemorrhage apart from perfusion deficits: neuronal mitochondrial injury? AJNR Am J Neuroradiol 2013;34:1535–41.
[48] Handa Y, Kabuto M, Kobayashi H, Kawano H, Takeuchi H, Hayashi M. The correlation between immunological reaction in the arterial wall and the time course of the development of cerebral vasospasm in a primate model. Neurosurgery 1991;28:542–9.
[49] Schneider UC, Schiffler J, Hakiy N, Horn P, Vajkoczy P. Functional analysis of Pro-inflammatory properties within the cerebrospinal fluid after subarachnoid hemorrhage in vivo and in vitro. J Neuroinflammation 2012;9:28.
[50] Kubota T, Handa Y, Tsuchida A, Kaneko M, Kobayashi H, Kubota T. The kinetics of lymphocyte subsets and macrophages in subarachnoid space after subarachnoid hemorrhage in rats. Stroke 1993;24:1993–2000.
[51] Rodriguez R, Baena Y, Gaetani P, Grignani G, Pacchiarini L. Effect of nimodipine on arachidonic acid metabolites after subarachnoid hemorrhage. Acta Neurol Scand 1987;76:267–71.
[52] Sehba FA, Schwartz AY, Chereshnev I, Bederson JB. Acute decrease in cerebral nitric oxide levels after subarachnoid hemorrhage. J Cereb Blood Flow Metab 2000;20:604–11.
[53] Woszczyk A, Deinsberger W, Böker D-K. Nitric oxide metabolites in cisternal CSF correlate with cerebral vasospasm in patients with a subarachnoid haemorrhage. Acta Neurochir (Wien) 2003;145:257–63.
[54] Kasuya H, Shimizu T. Activated complement components C3a and C4a in cerebrospinal fluid and plasma following subarachnoid hemorrhage. J Neurosurg 1998;71:741–6.
[55] Vergouwen MDI, Vermeulen M, Coert BA, Stroes ES, Roos YB. Microthrombosis after aneurysmal subarachnoid hemorrhage: an additional explanation for delayed cerebral ischemia. J Cereb Blood Flow Metab 2008;28:1761–70.
[56] Bosche B, Graf R, Ernestus RI, Dohmen C, Reithmeier T, Brinker G, et al. Members of the Cooperative Study of Brain Injury Depolarizations (COSBID). Recurrent spreading depolarizations after subarachnoid hemorrhage decreases oxygen availability in human cerebral cortex. Ann Neurol 2010;67:607–17.
[57] Dreier JP, Körner K, Ebert N, Görner A, Rubin I, Back T, et al. Nitric oxide scavenging by hemoglobin or nitric oxide synthase inhibition by N-nitro-L-arginine induces cortical spreading ischemia when K+ is increased in the subarachnoid space. J Cereb Blood Flow Metab 1998;18:978–90.
[58] Chaudhry NS, Orning JL, Shakur SF, Amin-Hanjani S, Aletich VA, Charbel FT, et al. Safety and efficacy of balloon angioplasty of the anterior cerebral artery for vasospasm treatment after subarachnoid hemorrhage. Interv Neuroradiol 2017;23:372–7.

[59] Patel AS, Griessenauer CJ, Gupta R, Adeeb N, Foreman PM, Shallwani H, et al. Safety and efficacy of noncompliant balloon angioplasty for the treatment of subarachnoid hemorrhage-induced vasospasm: A Multicenter Study. World Neurosurg 2017;98:189–97.
[60] Terry A, Zipfel G, Milner E, Cross DT, 3rd, Moran CJ, et al. Safety and technical efficacy of over-the-wire balloons for the treatment of subarachnoid hemorrhage-induced cerebral vasospasm. Neurosurg Focus 2006;15:E14 [21(3)].
[61] Choi BJ, Lee TH, Lee JI, Ko JK, Park HS, Choi CH. Safety and efficacy of transluminal balloon angioplasty using a compliant balloon for severe cerebral vasospasm after an aneurysmal subarachnoid hemorrhage. J Korean Neurosurg Soc 2011;49:157–62.