

Norepinephrine-induced hypertension dilates vasospastic basilar artery after subarachnoid haemorrhage in rabbits

Volker Neuschmelting · Ali-Reza Fathi · Eveline Teresa Hidalgo Staub · Serge Marbacher · Gerhard Schroth · Jukka Takala · Stephan M. Jakob · Javier Fandino

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Abstract

Background Vasopressor-induced hypertension is routinely indicated for prevention and treatment of cerebral vasospasm (CVS) after subarachnoid haemorrhage (SAH). Mechanisms underlying patients' clinical improvement during vasopressor-induced hypertension remain incompletely understood. The aim of this study was to evaluate angiographic effects of normovolaemic Norepinephrine (NE)-induced hypertension therapy on the rabbit basilar artery (BA) after SAH.

Methods Cerebral vasospasm was induced using the one-haemorrhage rabbit model; sham-operated animals served as controls. Five days later the animals underwent follow-up angiography prior to and during NE-induced hypertension.

Volker Neuschmelting and Ali-Reza Fathi contributed equally to the study.

V. Neuschmelting · A.-R. Fathi · S. Marbacher · J. Takala · S. M. Jakob · J. Fandino
Department of Intensive Care Medicine,
Bern University Hospital and University of Bern,
Bern, Switzerland

V. Neuschmelting · A.-R. Fathi · E. T. Hidalgo Staub · S. Marbacher · J. Fandino
Department of Neurosurgery,
Bern University Hospital and University of Bern,
Bern, Switzerland

G. Schroth
Institute of Neuroradiology,
Bern University Hospital and University of Bern,
Bern, Switzerland

A.-R. Fathi (✉)
Departments of Neurosurgery and Intensive Care Medicine,
University Hospital Berne,
3010 Berne, Switzerland
e-mail: AR.Fathi@gmx.net

Changes in diameter of the BA were digitally calculated in mean $\mu\text{m} \pm \text{SEM}$ (standard error of mean).

Findings Significant CVS of 14.2% was documented in the BA of the SAH animals on day 5 compared to the baseline angiogram on day 0 ($n=12$, $p<0.01$), whereas the BA of the control animals remained statistically unchanged ($n=12$, $p>0.05$). During systemic administration of NE, mean arterial pressure increased from 70.0 ± 1.9 mmHg to 136.0 ± 2.1 mmHg in the SAH group ($n=12$, $p<0.001$) and from 72.0 ± 3.1 to 137.8 ± 1.3 in the control group ($n=12$, $p<0.001$). On day 5 after SAH, a significant dilatation of the BA in response to norepinephrine could be demonstrated in both groups. The diameter of the BA in the SAH group increased from $640.5 \pm 17.5 \mu\text{m}$ to $722.5 \pm 23.7 \mu\text{m}$ ($n=12$, $p<0.05$;). In the control group the diameter increased from $716.8 \pm 15.5 \mu\text{m}$ to $779.9 \pm 24.1 \mu\text{m}$ ($n=12$, $p<0.05$).

Conclusion This study demonstrated that NE-induced hypertension causes angiographic dilatation of the BA in the SAH rabbit model. Based on these observations, it can be hypothesised that clinical improvement during vasopressor-induced hypertension therapy after SAH might be explained with cerebral vasodilatation mechanisms that lead to improvement of cerebral blood flow.

Keywords Subarachnoid haemorrhage · Cerebral vasospasm · Triple-H therapy · Induced hypertension · Norepinephrine

Abbreviations

| | |
|-----|----------------------------|
| CVS | Cerebral vasospasm |
| SAH | Subarachnoid haemorrhage |
| NE | Norepinephrine |
| BA | Basilar artery |
| SEM | Standard error of the mean |
| MAP | Mean arterial pressure |

| | |
|------|--|
| DIND | Delayed ischemic neurological deficits |
| CBF | Cerebral blood flow |
| DSA | Digital subtraction angiography |
| HHH | Haemodilution, hypervolaemia, induced hypertension |

Introduction

Delayed cerebral vasospasm (CVS) is considered the principal cause of high morbidity and mortality in patients undergoing treatment of subarachnoid haemorrhage [27], leading to delayed ischaemic neurological deficits (DIND), permanent neurological damage and death. It mainly transiently occurs 4–8 days after onset of SAH [5, 9, 14, 24]. Despite decades of research, the pathogenesis of CVS remains unclear [22].

Progress has been made in the management of CVS. Routine protocols combine early surgery with systemic administration of the calcium channel antagonist, nimodipine, and hyperdynamic therapy. As a result, the mortality and morbidity due to CVS have been reduced to 5–10%, compared to about 20% rates in the early 1980s [24].

Hyperdynamic therapy consists of haemodilution, hypervolaemia and induced hypertension (HHH), and is routinely administered despite some controversy [12, 14, 19, 24, 28]. The efficacy of haemodilution and hypervolaemia in particular has been seriously questioned lately [13, 17, 23, 24]. A relative risk of extracranial complications has been reported, and includes pulmonary oedema, hyponatraemia and congestive heart failure, to mention the most common. Induced hypertension, although associated with the possible risk of rebleeding from the aneurysm, has been evaluated as being safe [6, 16]. Vasopressors such as norepinephrine (NE) and phenylephrine are most commonly used clinically to induce hypertension during HHH therapy after SAH [14]. An improvement in patients' cerebral blood flow (CBF) and, thus, cerebral perfusion and clinical outcome has been documented in several studies [1, 8, 10, 17, 18, 23]. However, the mechanism underlying patients' enhanced clinical status remains incompletely understood. The aim of this study was to evaluate angiographic effects of normovolaemic NE-induced hypertension therapy on the rabbit BA after SAH.

Materials and methods

Study design

The protocol of this study was reviewed and approved by the Swiss Institutional Animal Care and Use Committee as

meeting the Swiss guidelines for laboratory animal use (approval #16/06). Twenty-four adult New Zealand White rabbits of either sex weighing 2.6–3.6 kg were randomly assigned to two experimental groups (12 animals each). One of these groups underwent experimental SAH on day 0, while the other served as a sham-operated control. All surgical procedures were performed under sterile conditions.

Angiography

After induction of general anaesthesia by intramuscular administration of ketamine (30 mg/kg) and xylazine (6 mg/kg), digital subtraction angiography (DSA) was performed on day 0 prior to SAH and on day 5 post SAH and sham-operation, respectively, in accordance with our protocol recently reported [15]. In brief, the rabbits' left (day 0) or right (day 5) subclavian artery was microsurgically cannulated using a catheter that was fixed distal to the vertebral branch. Subsequently, images of the vertebro-basilar system were obtained by rapid sequential DSA using intra-arterial bolus injection of non-ionic iopamidol (0.6 ml/kg) as contrast agent. Meanwhile, the arterial blood gas status was analysed to monitor ventilation parameters. The average diameter of the BA was digitally

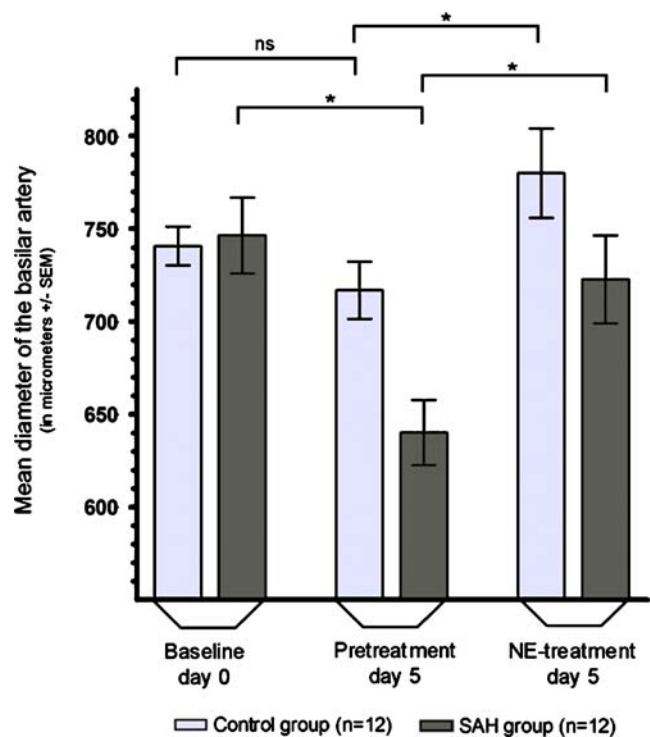


Fig. 1 Box plot showing the absolute change of the BA in diameter in SAH animals compared to controls (in $\mu\text{m} \pm \text{SEM}$): Baseline angiography on day 0 vs. pre-treatment follow up on day 5 vs. angiography during NE-induced hypertension on day 5. (* $p < 0.05$; ns non-significant)

Table 1 The effect of NE-induced hypertension on the rabbits' BA diameter in summary

| Exp group | n | State of treatment | BA diameter in μm (mean \pm SEM) | Δ BA diameter to previous state | | MAP in mmHg (mean \pm SEM) | Δ mean MAP to previous state | |
|-----------|----|--------------------|---|--|------|------------------------------|-------------------------------------|------|
| | | | | in μm | in % | | in mmHg | in % |
| control | 12 | baseline–day 0 | 740.6 \pm 10.4 | | | 73.9 \pm 2.8 | | |
| | | pretreatment–day 5 | 716.8 \pm 15.5 | 23.8 | 3.2 | 72.0 \pm 3.1 | 1.9 | 2.5 |
| | | NE-treatment–day 5 | 779.9 \pm 24.1 | 63.1* | 8.9 | 137.8 \pm 1.3 | 65.8*** | 91.4 |
| SAH | 12 | baseline–day 0 | 746.2 \pm 20.5 | | | 73.7 \pm 2.1 | | |
| | | pretreatment–day 5 | 640.5 \pm 17.5 | 105.7** | 14.2 | 70.0 \pm 1.9 | 3.7 | 5.0 |
| | | NE-treatment–day 5 | 722.5 \pm 23.7 | 82.0* | 12.9 | 136.0 \pm 2.1 | 66.0*** | 94.3 |

(* p <0.05, ** p <0.01, *** p <0.001)

calculated in μm using the automatic measurement tool of the ImagePro Discovery[®] analysis software (MediaCybernetics, Bethesda, MD, USA).

Cerebral vasospasm model

Following baseline DSA on day 0, the rabbits underwent the one-haemorrhage SAH rabbit model, as reported earlier by our group [4, 15]. Briefly, after draining of 1.0 ml cerebrospinal fluid, an equal amount of unheparinised autologous arterial blood was injected into the cerebro-medullary cistern under microscopic view to imitate SAH in order to induce CVS. An equal amount of isotonic saline solution was used instead in controls. Post-surgical pain relief was managed by subcutaneous administration of buprenorphine (0.1–0.2 mg/kg) for up to 36 h after SAH.

Induction of hypertension

After performance of pre-treatment follow-up DSA on day 5, peripheral hypertension was induced by continuous central arterial administration of NE (2.3–4.0 $\mu\text{g}\cdot\text{min}^{-1}\text{kg}^{-1}$) in dose-dependency to monitored blood pressure, the mean arterial pressure (MAP) in particular. Under constant conditions, a second follow-up DSA was performed to register any change of the BA diameter during peripheral hypertension.

Drugs

The following drugs were used: buprenorphinum (Temgesic[®] 0.3 mg/ml, Essex Chemie, Lucerne, Switzerland); iopamidol (Iopamiro[®] 300 mg/ml, Bracco, Milano, Italy); isoflurane (Forene[®] 99%, Abbott Laboratories, Abbott Park, IL, USA); ketamine HCl (Ketalar[®] 50 mg/ml, Pfizer AG, Zurich, Switzerland); norepinephrine (Noradrenalin Bichsel[®], Bichsel, Interlaken, Switzerland); sodium thio-

pental (Pentothal[®] 25 mg/ml, Abbott Laboratories, Abbott Park, IL, USA); and xylazine HCl (Xylapan[®] 20 mg/ml, Vetoquinol AG, Bern, Switzerland).

Statistical methods

Values were expressed as a mean in each group \pm SEM (n = number of animals). Statistical significance between 2 means and multiple means was determined by parametric One-way-ANOVA and Bonferroni's multiple comparisons post-testing, respectively. Statistical significance was con-

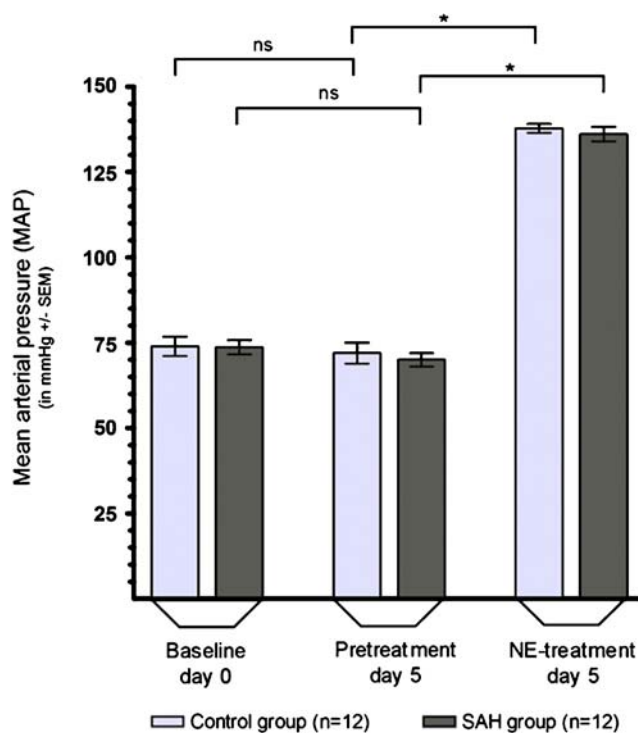


Fig. 2 Box plot showing the absolute MAP changes of the SAH group compared to controls (in mmHg \pm SEM): During baseline angiography on day 0 vs. pre-treatment follow up on day 5 vs. NE-induced hypertension on day 5. (* p <0.05; ns non-significant)

Table 2 Previous studies on induced hypertension therapy for treatment and prevention of CVS, ranked in order of scientific significance from least to most

| Study design | Authors | Trial randomised/controlled | N patients | Vasopressor | Induced blood pressure value in mmHg (MAP/SBP) | Additional hyperdynamic target | Therapeutic aim | Physiological end points | Results |
|---------------|--------------------------|-----------------------------|------------|---------------------------|--|---|-----------------|-------------------------------|---|
| Retrospective | Muizelaar JP et al. [18] | no/no | 4 | Phenylephrine | ~134 (MAP) | Hypervolaemia, Haemodilution | Treatment | CBF, clinical outcome | Increased CBF in 100%, good clinical outcome in 75% |
| | Kassell NF et al. [8] | no/no | 57 | Dopamine, Dobutamine | up to 150 (MAP) | Hypervolaemia | Treatment | DIND | Permanent improvement 74%, 16% unchanged |
| | Darby JM et al. [2] | no/yes | 13 | Dopamine | 111±13 (MAP) | - | Treatment | CBF | Enhanced CBF above ischaemic range in more than 90% of uninfarcted territories |
| Prospective | Yano K et al. [29] | no/no | 15 | Dobutamine | up to 200 (SBP) | Hypervolaemia, Haemodilution | Prevention | DIND | 20% developed DIND, 13% infarction |
| | Otsubo H et al. [21] | no/no | 41 | Dopamine, Dobutamine | 180 to 200 (SBP) | Cardiac output | Treatment | Clinical CVS, DIND | In 71% DIND improved, in 54% clinical vasospasm was reduced |
| | Awad IA et al. [1] | no/no | 42 | Dopamine | 160 to 200 (SBP) | Hypervolaemia, Haemodilution | Treatment | DIND | Normal 48%, minor deficits 33%, major deficits 19% |
| | Origitano TC et al. [20] | no/no | 43 | Dopamine | 180 to 200 (SBP) | Hypervolaemia, Haemodilution | Prevention | CBF, outcome | Increase in CBF by 30.1–47.2%; good outcome in 84% |
| | Solomon RA et al. [26] | no/no | 56 | Dopamine, Phenylephrine | unknown | Hypervolaemia | Prevention | DIND, outcome | 73% returned to premonibidic state without deficits |
| | Muench E et al. [17] | no/yes | 10 | Norepinephrine | 143±9.7 (MAP) | Hypervolaemia, Haemodilution | Treatment | CBF, brain tissue oxygenation | Increase in CBF at all time points (day 1, 3, 7 after SAH) |
| | Joseph M et al. [7] | no/yes | 16 | Phenylephrine, Dobutamine | 132.1 (MAP) | Hypervolaemia, Increase in cardiac output | Treatment | CBF | Increase in CBF from 19.2 to 33.7; similar enhancement of CBF during increased cardiac output by dobutamine |
| | Raabe A et al. [23] | no/yes | 45 | Dopamine, Norepinephrine | up to 220 (SBP) | Hypervolaemia | Treatment | Brain tissue oxygenation | Moderate hypertension: increase in brain tissue oxygenation in 90%, complications in 8% |
| | Egge A et al. [3] | yes/yes | 32 | Dopamine | 103.7±10.1 (MAP) | Hypervolaemia, Haemodilution | Prevention | Symptomatic CVS, CBF | No difference at 14 days, no difference at 1 year follow-up |

sidered if the P-value was less than 0.05 ($p < 0.05$) in context of the 95% confidence intervals of the difference examined (95% CI of diff).

Results

Arteriographic changes of the vessel diameter

On day 5 after SAH the diameter of the BA was significantly narrowed by $14.2 \pm 2.8\%$, to $640.5 \pm 17.5 \mu\text{m}$ in pre-treatment state compared to the baseline angiogram ($746.2 \pm 20.5 \mu\text{m}$) on day 0 ($n=12$, $p < 0.01$, 95% CI of diff: $37.4\text{--}175.0 \mu\text{m}$). In contrast, the BA diameter in controls was on average $740.6 \pm 10.4 \mu\text{m}$ wide on the baseline angiogram on day 0 and remained statistically unchanged to the pre-treatment state on day 5 ($716.8 \pm 15.5 \mu\text{m}$) ($n=12$, $p > 0.05$, 95% CI of diff: $-34.7 \mu\text{m}$ to $82.3 \mu\text{m}$). The SAH and control groups were, thus, significantly different from each other in diameter five days after the induction of SAH and the sham operation, respectively, prior to the administration of NE ($p < 0.05$, 95% CI of diff: $10.0\text{--}143.5 \mu\text{m}$) (Fig. 1).

Continuous administration of NE on day 5 in the SAH group caused significant arteriographic dilation of the spastic vessel by 12.97% to $722.5 \pm 23.7 \mu\text{m}$ in diameter ($n=12$, $p < 0.05$, 95% CI of diff: $13.8\text{--}150.2 \mu\text{m}$). In controls, the administered NE significantly dilated the BA by 8.86%, to $779.9 \pm 24.1 \mu\text{m}$ in relation to $716.8 \pm 15.5 \mu\text{m}$ in the pre-treatment state ($n=12$, $p < 0.05$, 95% CI of diff: $4.6\text{--}121.6 \mu\text{m}$). During continuous administration of NE on day 5, the groups did not statistically differ in BA diameter ($p > 0.05$, 95% CI of diff: $-9.4 \mu\text{m}$ to $124.1 \mu\text{m}$) (Fig. 1). The relative dilating effect on the BA diameter in the SAH group ($+12.97 \pm 2.52\%$) was also statistically insignificant in comparison to the relative effect of NE-induced hypertension detected in the BA of controls ($+8.86 \pm 2.66\%$, $n=12$, $p > 0.05$, 95% CI of diff: -3.67 to 11.8) (Table 1).

The initial blood gas parameters, such as $p\text{O}_2$ (54.8 ± 1.7 mmHg), $p\text{CO}_2$ (51.9 ± 1.2 mmHg) and pH (7.38 ± 0.01), did not change compared to the values monitored during follow-up angiography on day 5 in both the SAH ($p > 0.05$) and control groups ($p > 0.05$), and did not statistically differ between the two groups ($p > 0.05$).

Assessed changes of arterial blood pressure

During the baseline angiography on day 0, the MAP of the SAH group was at a level of 73.7 ± 2.1 mmHg ($n=12$). It remained statistically unchanged in comparison to its MAP pre-treatment assessment 5 days later (70.0 ± 1.9 mmHg, $p > 0.05$, 95% CI of diff: -3.2 to 10.5 mmHg). Correspondingly, controls showed similar MAP values. They started at a level of 73.9 ± 2.8 mmHg at baseline on day 0 and remained

statistically unchanged at 72.0 ± 3.1 mmHg in pre-treatment state on day 5 ($n=12$, $p > 0.05$, 95% CI of diff: -6.4 mmHg to 10.3 mmHg). In SAH animals, continuous administration of NE on day 5 induced a highly significant increase in MAP to 136.0 ± 2.1 mmHg ($n=12$, $p < 0.001$, 95% CI of diff: $59.2\text{--}72.9$ mmHg) compared to their pre-treatment state. Corresponding constant hypertension at a MAP level of 137.8 ± 1.3 mmHg was achieved in controls ($n=12$); it also showed a highly significant MAP rise compared to the time prior to the administration of NE on day 5 ($p < 0.001$, 95% CI of diff: $57.5\text{--}74.1$ mmHg) (Fig. 2).

The MAP level of the SAH group was similar to the level in controls throughout the pre-NE state within the 5 days the experiment lasted ($p > 0.05$). There was also no significant difference detected in the extent of induced hypertension between those two groups ($n=12$ each, $p > 0.05$, 95% CI of diff: -6.2 mmHg to 9.7 mmHg) (Table 1).

Discussion

Since it was first described in the 1970s, several studies have focused on the efficacy of vasopressor-induced hypertension therapy after SAH. The potency in both

The laminar flow through a pipe is physically described by the Hagen-Poiseuille law.

$$Q = \frac{\Delta P \pi r^4}{8 L \eta} = c \frac{\Delta P r^4}{\eta}$$

In terms of the CBF during CVS it states that the cerebral blood flow rate "Q" (= volume of blood flowing per unit time) is proportional to the arterial pressure difference "ΔP" between the pre- and postspastic part of the cerebral vessel and in proportional dependency to the fourth power of its radius "r". "L" is the length of the vessel and "η" the coefficient of blood viscosity. (For simplification the length "L" and the other constants are combined in constant "c".)

So far, the assumption to reason enhanced CBF observed in the state of induced hypertension was: By increasing MAP the increased arterial pressure difference alone results in enhanced CBF:

$$\uparrow Q = c \frac{(\uparrow \Delta P) r^4}{\eta}$$

Our results, however, suggest the increased CBF observed in previous studies during induced hypertension to be additionally caused by a dilative effect on the vessel diameter. Remarkable to mention is again its proportion to the CBF to the fourth power. Thus, small difference in diameter results in big difference in CBF.

$$\uparrow Q = c \frac{(\uparrow \Delta P) (\uparrow r)^4}{\eta}$$

Fig. 3 The Hagen-Poiseuille law of laminar flow is extrapolated to CBF and put in context to our results

prevention and treatment of CVS has been examined. The efficacy of the therapy as a preventive approach remains controversial due to conflicting data reported. While some authors observed in non-controlled, non-randomised trials that induced hypertension as part of HHH was beneficial in preventing CVS and DIND [20, 26, 29], Egge et al. was not able to repeat these finding in his prospective, controlled and randomised setting [3]. The preventive efficacy is thus considered questionable, with the need of induced hypertension therapy having been examined separately in a large, randomised, controlled clinical trial [14, 28].

However, vasopressor-induced hypertension is used routinely in the clinic and is—in contrast to the preventive approach—recommended for the treatment of clinical or angiographic CVS which is resistant to nimodipine [14, 24]. Support is based on several studies: three of them included additional hyperdynamic targets as part of HHH and concluded that there were benefits in the treatment of CVS in terms of enhancing CBF or improving clinical outcome [1, 8, 18]. Another five studies examined induced hypertension therapy separately from the haemodilutional and hypervolaemic approach and came to similar conclusions regarding its efficacy in terms of cerebral perfusion or neurological deficits (Table 2) [2, 7, 17, 21, 23]. In fact, hypertension has been demonstrated to be superior to hypervolaemia in its effectiveness [7, 17, 23]. Due to the lack of large, blinded, randomised and controlled trials on its efficacy in treating CVS, however, its scientific level of evidence has not exceeded level II.

The causes underlying the clinical observation of enhanced CBF and improved clinical outcome by vasopressor-induced hypertension in patients suffering from CVS have remained uncertain. During CVS the main cerebral vasculature resistance is shifted from the small arterioles to the narrowed major cerebral vessels. The vascular capacity of auto-regulation is impaired in the cerebral branches supplied by the narrowed arteries [11, 25]. CBF through the narrowed vessels thus becomes the limiting factor for the cerebral perfusion. Based on the Hagen-Poiseuille law of laminar flow, CBF may be manipulated by blood pressure gradient, vessel diameter and blood viscosity. So far, the enhanced CBF observed as a result of induced hypertension has been suggested to be dependent on the increase in blood pressure gradient alone [18, 21, 24]. Our data, however, demonstrate a significant dilatation of the narrowed vessels during NE-induced hypertension in an experimental SAH model. Therefore, we suggest that the clinical effect observed is additionally dependent on the dilating effect on the spastic vessel (Fig. 3). The significant increase in vessel diameter, along with the significant increase in blood pressure gradient, may, thus, cause the enhanced CBF and improved clinical outcome observed in the clinical studies during

vasopressor-induced hypertension. The mechanism itself of the dilatory effect of NE-induced hypertension on the vessel diameter remains unclear and is subject to further investigation. Hypothetically, a haemodynamic effect might be possible as consequence of direct adrenergic effects on the cerebral vasculature. The pathophysiology of CVS, however, is likely to play a minor role in the dilatory effect observed in our study. The relative dilatory effect of NE-induced hypertension on the BA in SAH animals was merely insignificantly greater than in controls.

Finally, some limitations of this study have to be mentioned. Firstly, the study is limited in providing data about a possible linear relation between blood pressure increase and vasodilatation effect due to single point assessment at high MAP values. Thus, our results are limited in serving for extrapolation to low and very moderate states of induced hypertension. Secondly, our study does not provide data evaluating the consistency over the time of the vasodilatation effects observed; this aspect is subject to further investigation.

Conclusion

This study demonstrates that NE-induced hypertension therapy significantly dilates the vasospastic basilar artery in a SAH rabbit model. This angiographic finding may possibly serve as an additional explanation for the enhanced CBF and improved clinical outcome observed during vasopressor-induced hypertension therapy in patients suffering from CVS.

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Financial disclosure/Conflict of interest

None of the authors has any conflict of interest to declare.

References

1. Awad IA, Carter LP, Spetzler RF, Medina M, Williams FC Jr (1987) Clinical vasospasm after subarachnoid haemorrhage: response to hypervolaemic haemodilution and arterial hypertension. *Stroke* 18:365–372
2. Darby JM, Yonas H, Marks EC, Durham S, Snyder RW, Nemoto EM (1994) Acute cerebral blood flow response to dopamine-induced hypertension after subarachnoid haemorrhage. *J Neurosurg* 80:857–864
3. Egge A, Waterloo K, Sjöholm H, Solberg T, Ingebrigtsen T, Romner B (2001) Prophylactic hyperdynamic post-operative fluid therapy after aneurysmal subarachnoid haemorrhage: a clinical, prospective, randomised, controlled study. *Neurosurgery* 49:593–605. discussion 605–596. doi:10.1097/00006123-200109000-00012

4. Fandino J, Sherman JD, Zuccarello M, Rapoport RM (2003) Cocaine-induced endothelin-1-dependent spasm in rabbit basilar artery in vivo. *J Cardiovasc Pharmacol* 41:158–161. doi:10.1097/00005344-200302000-00002
5. Ferguson S, Macdonald RL (2007) Predictors of cerebral infarction in patients with aneurysmal subarachnoid haemorrhage. *Neurosurgery* 60:658–667. discussion 667. doi:10.1227/01.NEU.0000255396.23280.31
6. Hoh BS, Ogilvy CS (2002) Risk of haemorrhage from unsecured, unruptured aneurysms during and after hypertensive hypervolaemic therapy. *Neurosurgery* 50:1207–1211. discussion 1211–1202. doi:10.1097/00006123-200206000-00006
7. Joseph M, Ziadi S, Nates J, Dannenbaum M, Malkoff M (2003) Increases in cardiac output can reverse flow deficits from vasospasm independent of blood pressure: a study using xenon computed tomographic measurement of cerebral blood flow. *Neurosurgery* 53(Joseph M, Ziadi S, Nates J, Dannenbaum M, Malkoff M):1044–1051 discussion 1051–1042
8. Kassell NF, Peerless SJ, Durward QJ, Beck DW, Drake CG, Adams HP (1982) Treatment of ischaemic deficits from vasospasm with intra-vascular volume expansion and induced arterial hypertension. *Neurosurgery* 11:337–343. doi:10.1097/00006123-198209000-00001
9. Kassell NF, Sasaki T, Colohan AR, Nazar G (1985) Cerebral vasospasm following aneurysmal subarachnoid haemorrhage. *Stroke* 16:562–572
10. Kosnik EJ, Hunt WE (1976) Post-operative hypertension in the management of patients with intracranial arterial aneurysms. *J Neurosurg* 45:148–154
11. Lang EW, Diehl RR, Mehdorn HM (2001) Cerebral auto-regulation testing after aneurysmal subarachnoid haemorrhage: the phase relationship between arterial blood pressure and cerebral blood flow velocity. *Crit Care Med* 29:158–163. doi:10.1097/00003246-200101000-00031
12. Lee KH, Lukovits T, Friedman JA (2006) “Triple-H” therapy for cerebral vasospasm following subarachnoid haemorrhage. *Neurocrit Care* 4:68–76. doi:10.1385/NCC:4:1:068
13. Lennihan L, Mayer SA, Fink ME, Beckford A, Paik MC, Zhang H, Wu YC, Klebanoff LM, Raps EC, Solomon RA (2000) Effect of hypervolaemic therapy on cerebral blood flow after subarachnoid haemorrhage: a randomised controlled trial. *Stroke* 31:383–391
14. Liu-Deryke X, Rhoney DH (2006) Cerebral vasospasm after aneurysmal subarachnoid haemorrhage: an overview of pharmacologic management. *Pharmacotherapy* 26:182–203. doi:10.1592/phco.26.2.182
15. Marbacher S, Neuschmelting V, Graupner T, Jakob SM, Fandino J (2008) Prevention of delayed cerebral vasospasm by continuous intrathecal infusion of glyceroltrinitrate and nimodipine in the rabbit model in vivo. *Intensive Care Med* 34:932–938. doi:10.1007/s00134-008-0995-x
16. Miller JA, Dacey RG Jr, Diring MN (1995) Safety of hypertensive hypervolaemic therapy with phenylephrine in the treatment of delayed ischaemic deficits after subarachnoid haemorrhage. *Stroke* 26:2260–2266
17. Muench E, Horn P, Bauhuf C, Roth H, Philipps M, Hermann P, Quintel M, Schmiedek P, Vajkoczy P (2007) Effects of hypervolaemia and hypertension on regional cerebral blood flow, intracranial pressure, and brain tissue oxygenation after subarachnoid haemorrhage. *Crit Care Med* 35:1844–1851. quiz 1852. doi:10.1097/01.CCM.0000275392.08410.DD
18. Muizelaar JP, Becker DP (1986) Induced hypertension for the treatment of cerebral ischaemia after subarachnoid haemorrhage. Direct effect on cerebral blood flow. *Surg Neurol* 25:317–325. doi:10.1016/0090-3019(86) 90205-3
19. Naval NS, Stevens RD, Mirski MA, Bhardwaj A (2006) Controversies in the management of aneurysmal subarachnoid haemorrhage. *Crit Care Med* 34:511–524. doi:10.1097/01.CCM.0000198331.45998.85
20. Origitano TC, Wascher TM, Reichman OH, Anderson DE (1990) Sustained increased cerebral blood flow with prophylactic hypertensive hypervolaemic haemodilution (“triple-H” therapy) after subarachnoid haemorrhage. *Neurosurgery* 27:729–739. discussion 739–740. doi:10.1097/00006123-199011000-00010
21. Otsubo H, Takemae T, Inoue T, Kobayashi S, Sugita K (1990) Normovolaemic induced hypertension therapy for cerebral vasospasm after subarachnoid haemorrhage. *Acta Neurochir (Wien)* 103:18–26. doi:10.1007/BF01420187
22. Pluta RM (2005) Delayed cerebral vasospasm and nitric oxide: review, new hypothesis, and proposed treatment. *Pharmacol Ther* 105:23–56. doi:10.1016/j.pharmthera.2004.10.002
23. Raabe A, Beck J, Keller M, Vatter H, Zimmermann M, Seifert V (2005) Relative importance of hypertension compared with hypervolaemia for increasing cerebral oxygenation in patients with cerebral vasospasm after subarachnoid haemorrhage. *J Neurosurg* 103:974–981
24. Sen J, Belli A, Albon H, Morgan L, Petzold A, Kitchen N (2003) Triple-H therapy in the management of aneurysmal subarachnoid haemorrhage. *Lancet Neurol* 2:614–621. doi:10.1016/S1474-4422(03) 00531-3
25. Soehle M, Czosnyka M, Pickard JD, Kirkpatrick PJ (2004) Continuous assessment of cerebral auto-regulation in subarachnoid haemorrhage. *Anesth Analg* 98:1133–1139. table of contents. doi:10.1213/01.ANE.0000111101.41190.99
26. Solomon RA, Fink ME, Lennihan L (1988) Early aneurysm surgery and prophylactic hypervolaemic hypertensive therapy for the treatment of aneurysmal subarachnoid haemorrhage. *Neurosurgery* 23:699–704
27. Suzuki M, Asahara H, Endo S, Inada K, Doi M, Kuroda K, Ogawa A (1999) Increased levels of nitrite/nitrate in the cerebrospinal fluid of patients with subarachnoid haemorrhage. *Neurosurg Rev* 22:96–98. doi:10.1007/s101430050038
28. Treggiari MM, Walder B, Suter PM, Romand JA (2003) Systematic review of the prevention of delayed ischaemic neurological deficits with hypertension, hypervolaemia, and haemodilution therapy following subarachnoid haemorrhage. *J Neurosurg* 98:978–984
29. Yano K, Kuroda T, Tanabe Y, Yamada H (1993) Preventive therapy against delayed cerebral ischaemia after aneurysmal subarachnoid haemorrhage: trials of thromboxane A2 synthetase inhibitor and hyperdynamic therapy. *Acta Neurochir (Wien)* 125:15–19. doi:10.1007/BF01401822