Eur J Appl Physiol (2010) 109:691–697
DOI 10.1007/s00421-010-1411-0

ORIGINAL ARTICLE

Active regulation of cerebral venous tone: simultaneous arterial and venous transcranial Doppler sonography during a Valsalva manoeuvre

Erwin Stolz · Damian A. W. Rüsges · Oskar Hoffmann · Tibo Gerriets · Max Nedelmann · Piergiogio Lochner · Manfred Kaps

Accepted: 15 February 2010 / Published online: 7 March 2010

Abstract The aim of this study was to analyse the cerebral venous outflow in relation to the arterial inflow during a Valsalva manoeuvre (VM). In 19 healthy volunteers (mean age 24.1 ± 2.6 years), the middle cerebral artery (MCA) and the straight sinus (SRS) were insonated by transcranial Doppler sonography. Simultaneously the arterial blood pressure was recorded using a photoplethysmographic method. Two VM of 10 s length were performed per participant. Tracings of the variables were then transformed to equidistantly re-sampled data. Phases of the VM were analysed regarding the increase of the flow velocities and the latency to the peak. The typical four phases of the VM were also found in the SRS signal. The relative flow velocity (FV) increase was significantly higher in the SRS than in the MCA for all phases, particularly that of phase IV ($p < 0.01$). Comparison of the time latency of the VM phases of the MCA and SRS only showed a significant difference for phase I ($p < 0.01$). In particular, there was no significant difference for phase IV (15.8 ± 0.29 vs. 16.0 ± 0.28 s). Alterations in venous outflow in phase I are best explained by a cross-sectional change of the lumen of the SRS, while phases II and III are compatible with a Starling resistor. However, the significantly lager venous than the arterial overshoot in phase IV may be explained by the active regulation of the venous tone.

Keywords Ultrasound · Autoregulation · Valsalva manoeuvre · Cerebral veins

Communicated by Keith George.

E. Stolz and D. A. W. Rüsges contributed equally to this study.

E. Stolz (✉) · D. A. W. Rüsges · T. Gerriets · M. Nedelmann · P. Lochner · M. Kaps
Department of Neurology, Justus-Liebig University, Am Steg 14, 35385 Giessen, Germany
e-mail: erwin.stolz@neuro.med.uni-giessen.de

D. A. W. Rüsges
Department of Internal Medicine, Inselspital, University of Bern, Bern, Switzerland

O. Hoffmann
University of Applied Sciences, Giessen, Germany

Introduction

The Valsalva manoeuvre (VM) causes transient profound changes of systemic and cerebral blood flow (Appenzeller and Oribe 1997; Tiecks et al. 1995a, b). VM occurs commonly during normal life. It may result in "blackout", i.e. when lifting a heavy weight or when coughing. Primarily based on the change of systemic arterial blood pressure (ABP), the VM is subdivided into four phases (Appenzeller and Oribe 1997): at the onset of straining an increase of ABP is observed due to compression of the aorta (phase I). While the subject forcefully strains against resistance, intrathoracic pressure increases, venous return, cardiac output and ABP fall (phase II). Phase II can be subdivided into two components, a phase IIa where ABP initially decreases to a minimum followed by a transient increase in phase IIb. Once the strain ends, intrathoracic pressure falls and pulmonary venous capacitance rises leading to a fall in ABP below baseline which is counteracted by baroreceptor action. In phase IV ABP rises transiently beyond baseline (which is referred to as "overshoot"). There is sufficient evidence that phase IV of the VM is dominated by a sympathetic stimulation because the overshoot can be blocked pharmacologically or by sympathectomy (Schroeder et al. 2009; Zhang et al. 2004).

Tiecks et al. (1995a, b) systematically studied the effect of VM on the intracranial arterial circulation and developed an explanatory model for the effects observed. In short, in phase I the sudden rise of the intrathoracic pressure causes a rise of cerebrospinal fluid and central venous pressure and hence of the intracranial pressure (ICP) resulting in only a slight increase of arterial blood flow velocities (ABFV) despite a sudden increase of ABP (Greenfield et al. 1984; Hamilton et al. 1936, 1944). With sustained high ICP and falling ABP in phase IIa the ABFV falls. Activation of the baroreceptor reflex and cerebral autoregulation in phase IIb result in an increase of ABP and ABFV. While a clear minimum of ABFV marks phase IIa in averaged tracings, phase IIb often is only recognisable as plateau before ABFV drops in phase III (Pott et al. 2000; Tiecks et al. 1995a, b; Zhang et al. 2004). After release of the strain, ABP transiently drops in phase III, but a similar drop in magnitude of ABFV is usually not observed due to cerebral autoregulation. Both the ABP and ABFV display an overshoot in phase IV, which in magnitude is significantly higher for the ABFV. This overshoot in ABFV can also be blocked pharmacologically or by sympathectomy (Schroeder et al. 2009; Zhang et al. 2004).

Venous outflow in relation to arterial inflow during VM has not been studied systematically before, although the venous compartment contains about 70% of the total intracranial blood volume (Shenkin and Bouzarth 1970; Ropper and Rockoff 1993), and hence may be important for intracranial blood volume control. Usually intracranial veins are regarded as pure capacitance vessels. Existing models on cerebral venous outflow (CVO) seem to support this view. A widely accepted hypothesis is that CVO is governed by a Starling resistor (Luce et al. 1982), i.e. CVO depends on the difference between ABP and ICP and hence of the cerebral perfusion pressure (CPP). However, data have been reported which indicate that intracranial veins may possess an active regulation which in a teleological sense is likely to be directed on intracranial blood volume control.

Histological evidence of a dense aminergic innervation of cerebral veins (Cuevas et al. 1994; Asada and Lee 1992) and the experimental results which indicate a stronger venous than arterial vasoconstriction upon sympathetic stimulation with a short latency to stimulus onset (Auer et al. 1981) seem to support the concept of the active venous volume regulation and prompted the clinical studies in patients with traumatic brain oedema, who showed reduction of intracranial pressure (ICP) when treated with dihydroergotamine (Asgeirsson et al. 1994, 1995). However, these results could not be reproduced in patients with tumour oedema (Bundgaard et al. 2001). The inconclusive clinical effect of aminergic stimulation and the general histological lack of smooth muscle cells in cerebral veins (Cervós-Navarro and Roggendorf 1983) rendered the hypothesis of active venous cerebral volume control unlikely until recently. The discovery of a venous cuff mechanism consisting of collagen fibres (Pang et al. 2001) and smooth muscle cells (Vignes et al. 2007; Dagain et al. 2009) at the entrance of the bridging veins to the sinuses revived the hypothesis of active venous volume control.

The aim of this study was to describe CVO during VM in relation to the cerebral arterial inflow. The VM was chosen because it contains components which are governed by the passive hydromechanical changes and components based on active counter-regulation. As already pointed out above, particularly phase IV of the VM is dominated by a sympathetic stimulation. By comparing the cerebral arterial inflow with the venous outflow, the effect of active venous outflow regulation could either consist of increased venous outflow and/or a short arterio-venous latency well below the capillary passage time.

Methods

Volunteers

This study was approved by the appropriate ethical committee, and each participant gave written informed consent. Nineteen healthy volunteers (mean age 24.1 ± 2.6 years, 11 females, 8 males) took part in this study. Forty-five volunteers without a history of cardiovascular disease, hypertension, or pregnancy had to be screened prior inclusion; however, 24 (53%) had to be excluded because of an insufficient occipital acoustic bone window, which did not allow for a sufficient signal quality over a period of 15 min. Two participants had to be excluded post hoc. In one the straining phase of VM was too short, in the other—despite all precautions—an arterial signal was mistaken for the straight sinus.

Measurement of physiological variables

Venous and arterial blood flow velocities (FVs) were recorded with a Multi Dop X ultrasound system (DWL, Sipplingen, Germany). Two 2-MHz transducers were mounted on an individually fitted head frame. The middle cerebral artery (MCA) was recorded through the temporal acoustic bone window at an insonation depth of 54–48 mm (Aaslid et al. 1982). In order to examine the straight sinus (SRS), a second probe was mounted on the occipital acoustic bone window 1–4 cm paramedian and about 1–3 cm above the external occipital protuberance as described earlier (Rosengarten et al. 2002; Stolz et al. 2009). A venous signal was ascertained in an examination depth of 46–58 mm by its prompt reactivity to a Valsalva manoeuvre.

Arterial blood pressure was measured using a non-invasive finger blood pressure monitor (Finapres 2300, Ohmeda, USA). This device uses a photoplethysmographic method and fast cuff servo system to keep the diameter of the finger arteries constant. Care was taken that the pressure cuff was always located at the height of the right atrium. To exclude hyper- or hypoventilation before the VM, the endexpiratory pCO_2 was measured with a capniometer (DWL, Sipplingen, Germany). All variables were recorded simultaneously and analysed off-line.

During measurements all volunteers were lying horizontally on their sides in a quiet room. The experiment consisted of an initial baseline phase of 10 min of which the last 2 min were recorded. Then all participants performed a VM of 10 s duration starting from a normal inspiration. After another baseline phase of 2 min, the VM was repeated. In order to increase the reproducibility of the VM, the manoeuvre was practiced with the participants before the start of the experiment. For all VMs, the subjects aimed at a pressure of 40 mmHg when blowing into a tube attached to a manometer. This was aided through the use of bio-feedback. The start and end of the VM was marked by an acoustic signal.

Data analysis

Analogue signals were digitised with a sample rate of 57.4 Hz using the ultrasound's analogue to digital converter. Off-line analysis was performed with a dedicated software (Digital Signal Processor, V2.01, O. Hoffmann, University of Applied Sciences, Giessen) resulting in time-averaged mean values for ABP, arterial and venous FVs for each cardiac cycle. Tracings of the variables were transformed to equidistantly re-sampled data at 40 Hz (equidistant data points in 0.025 s distance) by linear interpolation. ABP, venous and arterial FVs of the two VMs were averaged triggered by the onset of the ABP deflection from baseline (Microcal Origin 8.0, Origin Lab Corporation, Northampton, USA). This was done for the absolute values and the relative response related to the preceding baseline. The relative change of variables (Va) related to the baseline was calculated using the following formula: $Va_{rel} = 100(Va - Va_{baseline})/Va_{baseline}$.

Descriptive statistics is given as mean and standard error. The VM response was divided into four phases (I–IV). The coefficient of variation was calculated for the absolute values of ABP and venous and arterial FVs for the peaks of phases I–IV. The time latencies to and the relative FV increase of the different phases were measured in the individual recordings of the participants and were compared with a non-parametric Mann–Wilcoxon *U* test. The intraindividual reproducibility of the two VM was analysed using a method described by Bland and Altman (1986) resulting in 2 SD CI).

Results

The recordings of the ABP and MCA FV signals showed the typical phases I–IV described and defined above (Fig. 1a–d). Four phases of the VM were also found in the SRS FV signal (Fig. 1e–f). The absolute and relative changes in ABP and intracranial VFs are summarised in Table 1. Table 2 contains the coefficients of variation and the 2 SD CI for the intraindividual reproducibility. Both were highest for phase IV of all examined variables.

The relative FV increase was significantly higher in the SRS than in the MCA for all phases, particularly that of phase IV ($p < 0.01$; Table 1). The relative overshoot in phase IV related to the baseline values was double as high for the SRS than for the MCA (Fig. 2). Table 3 contains the times to the individual peaks from start of VM. The ABP signal was—except for phase IIb—significantly preceded by all other phases of the MCA response. Also the time latency of phases I, IIa and IV of the SRS signal significantly preceded the corresponding phases of the ABP response. Comparison of the time latency of the VM phases of the MCA and SRS only showed a significant difference for phase I ($p < 0.01$). In particular, there was no significant difference for phase IV (peak 15.8 ± 0.29 vs. 16.0 ± 0.28 s; Fig. 2).

Discussion

The explanation of the behaviour of the venous outflow during VM we observed in this study is challenging. While the recordings of ABP and MCA FV comply well with the results of other studies (Tiecks et al. 1995a, b; Pott et al. 2000; Zhang et al. 2004), no previous studies have been undertaken so far to study CVO during a Valsalva manoeuvre.

Phases I and IIa of the venous recording are similar to the ABP course in direction and magnitude of the relative change from baseline and approximately six times higher than in the MCA in phase I. Particularly phase I in the SRS precedes that of the ABP signal. This behaviour cannot be reconciled with a Starling resistor model which has been assumed to describe the cranial venous outflow and would predict the dependence of the venous outflow from the cerebral perfusion pressure (CCP) (Luce et al. 1982). In this case, with an increase of the ICP and the arterial inflow pressure, cerebral venous outflow should only modestly increase or even fall with venous flow velocities being reduced. It is more plausible that the sudden ICP increase in phase I is caused by a partial collapse of the straight sinus with inward bulging of the walls resulting in increased flow velocities. Data on the ICP during VM are scarce. Greenfield et al. (1984) observed an ICP increase of

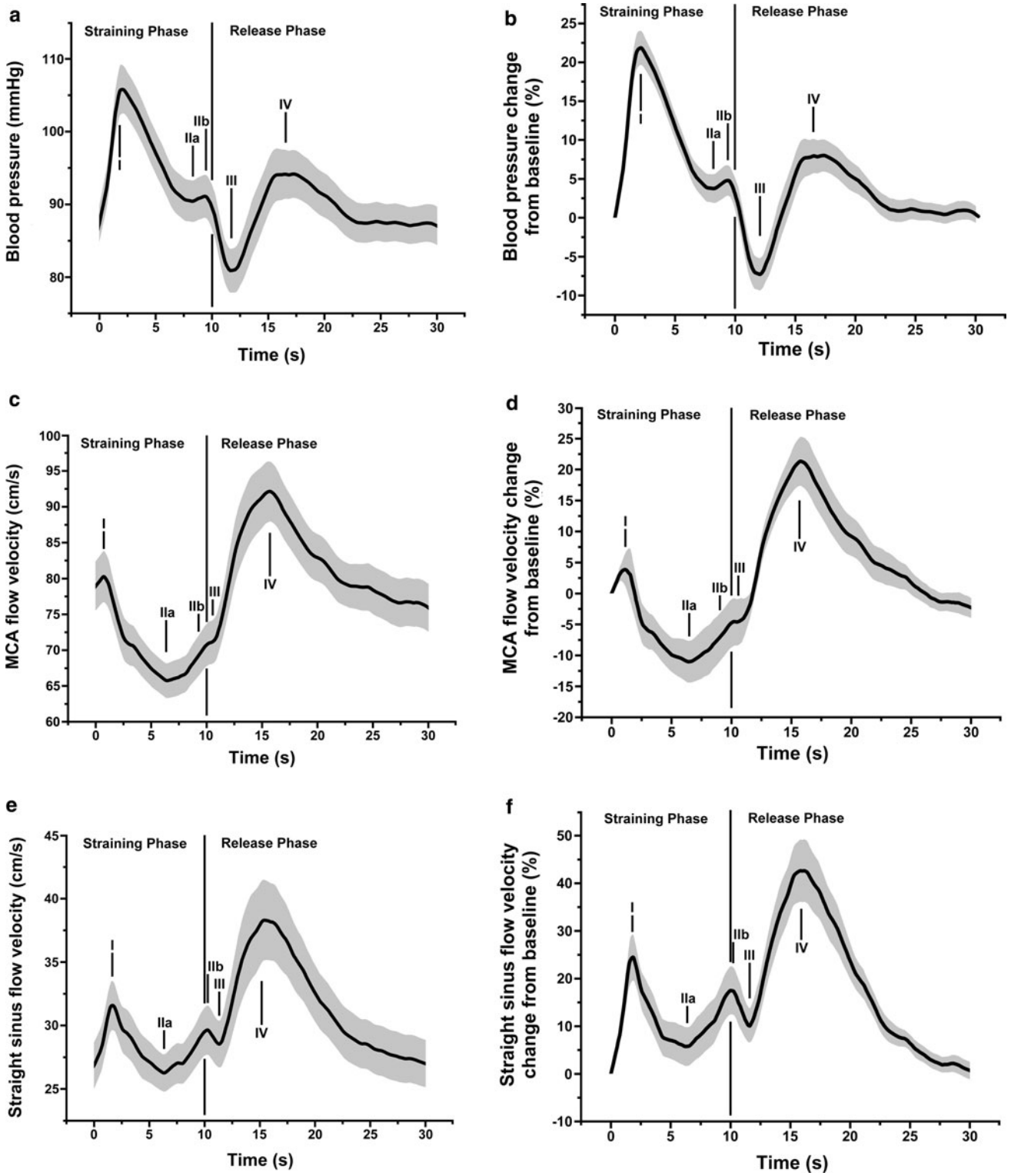

Fig. 1 Time course of blood pressure, middle cerebral and straight sinus flow velocity changes over time. The *grey shaded area* gives the standard error. *Upper row* changes of blood pressure: **a** absolute, **b** relative. *Middle row* changes of middle cerebral artery flow velocity: **c** absolute, **d** relative. *Bottom row* changes of straight sinus flow velocity: **e** absolute, **f** relative

more than 40% during phase I and a VM of 20 mmHg strength. A partial sinus collapse under conditions of marked ICP increase has been described in humans (Osterholm 1970; Martins et al. 1974). Phase II is characterised by a sustained increase of ICP (Greenfield et al. 1984). During phase IIa the drop in ABFV would result in a

Table 1 Absolute and relative changes of arterial blood pressure (ABP), middle cerebral artery (MCA) and straight sinus (SRS) flow velocities

	Baseline	Phase				
		I	IIa	IIb	III	IV
Absolute values						
ABP (mmHg)	87.4 ± 2.6	105.8 ± 3.3	90.5 ± 2.9	91.1 ± 2.9	80.9 ± 3.1	94.2 ± 3.3
MCA FV (cm/s)	78.9 ± 3.5	79.8 ± 3.6	65.8 ± 2.5	70.8 ± 3.0	71.3 ± 3.1	92.1 ± 4.2
SRS FV (cm/s)	26.9 ± 1.9	31.5 ± 1.9	26.28 ± 1.5	29.6 ± 2.0	29.0 ± 2.1	38.2 ± 3.1
Relative change						
ABP (%)	0	21.9 ± 2.3	3.7 ± 1.9	4.8 ± 2.0	−7.3 ± 2.1	8.0 ± 2.1
MCA FV (%)	0	3.8 ± 2.5	−11.0 ± 3.4	−4.7 ± 3.9	0.0 ± 2.0	21.3 ± 4.0
SRS FV (%)	0	24.5 ± 4.9*	5.7 ± 4.1*	17.5 ± 5.1*	10.0 ± 3.8^{+}	42.7 ± 6.6*

The relative change of FVs in the MCA was compared with that in the SRS (* $p < 0.01$, $^{+}$ $p < 0.05$)

Table 2 Coefficients of variation and intradindividual reproducibility of measurements

	Baseline	Phase				
		I	IIa	IIb	III	IV
Coefficient of variation						
ABP	0.19	0.19	0.20	0.21	0.25	0.22
MCA FV	0.28	0.27	0.23	0.27	0.30	0.29
SRS FV	0.44	0.38	0.37	0.42	0.48	0.51
Intraindividual reproducibility (2 SD CI)						
ABP (mmHg)	9.82	19.72	15.86	18.98	22.64	15.24
MCA FV (cm/s)	12.94	19.34	13.00	28.62	21.14	13.80
SRS FV (cm/s)	8.20	9.84	9.34	17.52	11.78	10.62

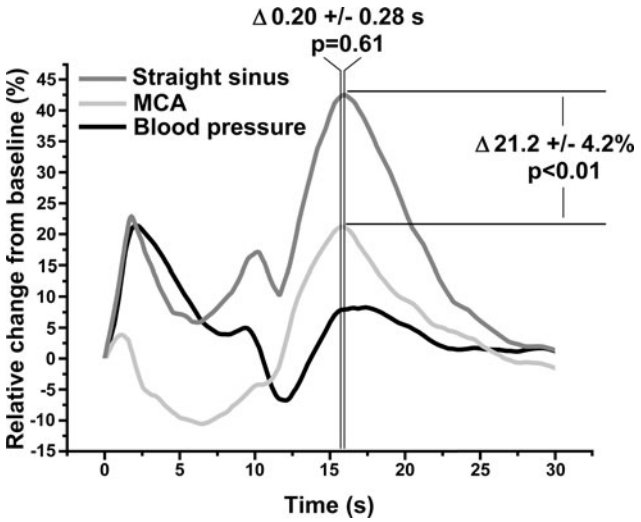

Fig. 2 Synopsis of the time course of the relative changes of blood pressure, middle cerebral artery and straight sinus flow velocities over time. The displayed differences relate to the middle cerebral artery and the straight sinus

reduced and in phase IIb—with arterial autoregulation setting in—in an increased venous outflow. However, this precludes a preserved Starling resistor with a waterfall flow, i.e. CVO is only dependent on the CPP and not the downstream pressures. Since venous peak latencies do not lag behind the ABP and MCA signals, ICP seems to be the key denominator in these phases with venous flow governed by hydromechanics and not active regulation. Similarly, phase III can be explained by a waterfall behaviour caused by a change of CPP.

Regarding CVO, the most interesting results are found in phase IV. In this phase ICP has almost returned to baseline (Greenfield et al. 1984). Therefore, there is no reason to assume a cross-sectional deformation of the SRS lumen. With increased cross-sectional lumen Hagen–Poiseuille's law would predict a decrease of flow velocities in the SRS, rather than an increase. Although the increase of arterial inflow increases the CPP, the venous overshoot is larger than the cerebral arterial by a factor >100% related to the baseline ($p < 0.01$). This finding cannot be explained by a Starling resistor, because in this case the relative overshoot would be in the order of the arterial inflow. This difference is also not an effect of the insonation angle, because using relative changes of flow velocities abolishes the influence of the insonation angle. Further, there is no detectable time delay between the arterial and venous peak IV, so that indeed a sympathetic venoconstriction is a possible explanation for this behaviour. In the introduction, it was already outlined that cerebral veins possess a dense aminergic innervation and recently a cuff mechanism at the entrance of the bridging veins to the sinus consisting of collagen fibres and smooth muscles has been discovered (Dagain et al. 2009). Differences in the main extracranial venous run-off route have also to be considered. In the supine position the jugular venous system serves as the main drainage route, during standing the vertebral venous plexus (Valdueza et al. 2000). However, in both cases the SRS is the main intracranial drainage pathway. Other alternative routes (ophthalmic veins, diploic veins, plexus caroticus, etc.) play no significant role due to their small cross-sectional area.

Table 3 Time to peak from baseline for the arterial blood pressure (ABP), middle cerebral artery (MCA) and straight sinus (SRS) flow velocity signals

Time to peak (s)	Baseline	Phase				
		I	IIa	IIb	III	IV
ABP	0	2.2 ± 0.14	7.7 ± 0.19	9.7 ± 0.15	12.3 ± 0.20	17.1 ± 0.33
MCA (s)	0	1.3 ± 0.09*	6.1 ± 0.29*	9.5 ± 0.28^{ns}	11.5 ± 0.27*	15.8 ± 0.29*
SRS FV (s)	0	1.8 ± 0.13*/*	6.5 ± 0.22*/ns	10.1 ± 0.16$^{ns/ns}$	11.9 ± 0.18$^{ns/ns}$	16.0 ± 0.28$^{+/ns}$

The MCA signal was compared with the blood pressure signal (**$p < 0.01$, *ns* not significant). The SRS signal was compared with the ABP ($^{*/-}p < 0.01$, $^{+/-}p < 0.05$, *ns*/- not significant) and the MCA signal ($^{-/*}p < 0.01$, -/*ns* not significant)

Since the effects observed in this study affect the cerebral circulation as a whole, it is justified to assume the induced changes in the MCA and the SRS to be representative of the arterial and venous cerebral circulation, as was proposed by Ursino and Lodi (1997). Of course our findings are not a proof for an active regulation of venous tone considering the limitations of the study. A shortcoming of this study is the lack of information on the cross-sectional area of the SRS (and middle cerebral artery) and of the ICP. However, conventional imaging methods such as magnetic resonance imaging do neither have a sufficient spatial nor time resolution to study this question in humans. ICP measurements in healthy humans are also difficult to accomplish. On the other hand, the high drop-out rate in this study in healthy young people due to insufficient acoustic penetration makes it difficult to apply this setup in clinical situations.

We know that our interpretation of data is speculative. At least we did not find results which outrightly would contradict an active regulation of venous tone. If cerebral veins possess an active regulation of tone, it aims at intracranial blood volume control. Naturally, medical manipulation of this mechanism would be a new aspect of treatment of raised intracranial pressure. We hope that our results stimulate further research in this area.

In conclusion, alterations in the venous outflow in phase I of the VM observed in this study are best explained by a cross-sectional change of the lumen of the SRS, while phases II and III are compatible with a Starling resistor. The significantly lager relative venous than the arterial overshoot in phase IV might be interpreted as a result of the active regulation of the venous tone.

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