Vasopressin increases Cerebral Perfusion Pressure but not Cerebral Blood Flow in Neurosurgical Patients with Norepinephrine-Refractory Hypotension: A Preliminary Evaluation using the non-invasive Quantix ND in Comparison to the Literature

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Abstract

The maintenance of sufficient mean arterial pressure (MAP) to sustain perfusion and oxygen delivery to all major organs is important patients in intensive care but for neurosurgical patients after SAH or TBI it is essential to avoid secondary brain damage or delayed ischemia. So far most neurosurgical intensive care units use intracranial pressure (ICP) and cerebral perfusion pressure (CPP) as therapy guidance for those patients. Use of fluid resuscitation and norepinephrine is standard to achieve CPP between 50–70 mmHg. But sometimes norepinephrine-refractory hypotension occurs. In those cases, arginin-vasopressin (AVP) is often the drug of choice. AVP and its synthetic analogies are widely used in modern medicine and gained interest in treatment of septic shock or refractory hypotension after cardiac surgery or hypovolemic shock. Recent papers also showed a significant impact of AVP in resuscitation of after traumatic brain injury (TBI) and influence on CPP in TBI patients during ICU treatment. But little is known about the effects of AVP on cerebral perfusion and oxygenation. The present preliminary study was carried out to examine the influence of vasopressin administration on cerebral blood flow by using the non-invasive QuantixND® device. We found significantly increased MAP and CPP but no concomitant elevation in CBF. In contrast, in most patients the CBF even decreased despite elevation of CPP. We conclude that AVP is an alternative drug to maintain MAP and CPP but must be used with care in patients with already compromised cerebral perfusion.

Introduction

The means of treatment of ICU patients is to sustain perfusion and O_2 delivery to all major organs to avoid organ damage. Since it is not possible to influence the initial insult on neurosurgical ICUs it is crucial to prevent an additional neuronal damage. Thus, avoidance of early brain injury (EBI) following aneurysmal subarachnoid [1], raised intracranial pressure (ICP) or low cerebral perfusion pressure (CPP) due to low mean arterial blood pressure (MAP) following traumatic brain injury is key. Especially in aSAH patients suffering from cerebral vasospasm (CV) often leads to sequelae like delayed cerebral ischemia (DCI) or low tissue oxygenation [2]. To minimize the risk of brain ischemia, standard treatment guidelines have been established including the maintenance of a CPP > 60 mmHg. The management of CPP normally includes the control of ICP and mean arterial pressure (MAP), since CPP = MAP-ICP. Despite many clinical trials so far, no level I evidence for an ideal CPP exists, but the guidelines of the Brain Trauma Foundation recommend a CPP between 50–70 mmHg in traumatic brain injury (TBI) patients, depending on the patient's individual cerebral hemodynamic profile [3]. For patients suffering from aneurysmal subarachnoid hemorrhage (aSAH) there might be completely different needs for CPP levels since the major cause of death after SAH is DCI often due to cerebral vasospasm and thus elevated vascular resistance [4,5]. For those patients among other treatment needs, a sufficient CCP is crucial [6]. To obtain CPP, fluid resuscitation can be used but, in most patients, additionally vasopressors are needed. Today catecholamines are the agent of choice. But with increasing dosage or prolonged duration, side effects like increased heart rate and increased myocardial oxygen consumption occur. Those side effects can potentiate the extracranial effects of SAH like intravascular volume depletion or cardiac impairment

known as neurogenic myocardial injury (NMI) [7,8]. The elevation of systemic vascular resistance can also compromise end organ perfusion [9,10]. In addition, refractoriness to catecholamines exists [11]. For those patients, arginine-vasopressin (AVP) might be the drug of choice.

Vasopressin is synthesized as a prehormone in the magnocellular neurons of paraventricular and supraoptic nuclei of the hypothalamus and is one of the key players for osmotic and cardiovascular hemostasis [12]. It is cleaved into the active hormone and released into systemic circulation from the posterior pituitary gland. The serum levels of this nonapeptide represent the interaction of AVP synthesis, release, and metabolism. Arginine vasopressin exerts its actions via a variety of receptors. The main three receptors are: AVPR1a (V1 receptor, mainly vascular functions), AVPR1b (V3 receptor, mostly central functions) and AVPR2 (V2 receptor, renal functions). In addition, AVP can act via oxytocin receptors as well as purinergic receptors [13]. The V3 receptor is expressed in the hippocampus and the anterior pituitary gland and V3 receptor stimulation by vasopressin leads to a release of adrenocorticotropic hormone (ACTH) and thus interacts with the corticosteroid axis in response to stress such as hypotension [14,15].

The regulation of the vasoconstrictive effects of AVP is an interplay of various actions and receptors. AVPR1a, a G-protein coupled receptor, is the main effector for the AVP associated vasocontraction and is expressed on the vascular smooth muscle cell, platelets, and hepatocytes for review see [16]. It stimulates a phosphatidyl-inositol-calcium signal pathway leading to smooth muscle contraction [13]. But on the other side AVPR1a stimulation also causes production of nitric oxide, a potent vasodilator in pulmonary [17] and coronary vessels [18]. Also, the stimulation of oxytocin receptors by low dose vasopressin can induce vasodilation [19].

Due to the mostly independently regulated pathways of the different AVP receptors, synthetic agonists of the AVP receptors are routinely used in modern medicine, e.g. desmopressin, a V2 receptor agonist is used in diagnostics and treatment of diabetes insipidus or used for treatment of coagulopathies [20]. Vasopressin or terlipressin (via V1 receptor) are used in postoperative bowel distention or refractory hypotension after cardiac surgery [21]. AVP gained more interest over the years in treatment of vasoplegic septic shock or other forms of refractory vasoplegic catecholamine resistant shock [13,16]. AVP can restore vascular tone by at least four different mechanisms: activation of AVPR1a, modulation of NO, modulation of ATP-sensitive K^+channels and potentiation of adrenergic vasoconstrictive agents leading to contraction of small arterioles and increasing peripheral vascular resistance [22].

A review of literature by Russel in 2011 showed that in patients with septic shock the use of low dose vasopressin combined with corticosteroids had better patient outcome than norepinephrine and steroids but showed potential side effects such as peripheral ischemia or disturbances in microcirculation. Even though studies clearly showed that AVP is safe to use and can have beneficial effects in septic shock [13,16] or in traumatic shock resuscitation when combined with low fluid resuscitation [9,20,23] so far validated recommendations in clinical guidelines for the use of AVP in either septic shock or resuscitation fail to appear.

The use of AVP in neurosurgical or neurological patients is even more controversial. After brain injury vasopressin is released leading to inflammatory reactions and cerebral edema [24]. Use of AVPR1a antagonists led to attenuation of secondary brain lesion and edema [25,26]. Interestingly in a model for blunt trauma to the head and chest showed that the use of AVP was as effective as phenylephrine to maintain CPP but improved ICP and cerebral tissue oxygenation [27]. In 2013 Van Haren et al. published a paper concerning the use of vasopressin for CPP management in patients with severe traumatic brain injury [28]. They concluded that vasopressin is safe to use and represents an effective alternative to catecholamines for maintaining CPP.

Since the vasoconstrictive potency of AVP is well known and the study by Van Haren et al. didn't measure cerebral blood flow (CBF) or brain tissue oxygenation ($P_{bt}O_2$) the present preliminary study was carried out to evaluate the influence of AVP on CPP, ICP and CBF in neurosurgical patients suffering from catecholamine refractory hypotension.

Materials and Methods

Ethics/ IRB Statement

This retrospective study was approved by the Local Ethics Committee University of Regensburg Approval Number 18-1059-104.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1975 Helsinki declaration and its later amendment. For the present retrospective study informed consent is not required.

Patient selection and ICU therapy:

We included 5 patients on our neurosurgical ward in this preliminary study. Four patients were treated for aSAH and one patient for severe TBI (for patient demographics see table 1). The localization of the aneurysm responsible for the SAH and severity of the bleeding was documented according to the classification of the World Federation of Neurological Surgeons (WFNS) who showed a norepinephrine refractory hypotension. All patients had continuous ICP monitoring (Raumedic Neurovent®, Raumedic AG, Helmbrechts, Germany) and intraarterial blood pressure measurement to continuously calculate CPP. Also, $P_{bt}O_2$ values were measured using the Licox® probe (Integra Life Science, Tullamore, Ireland) according to our standard protocols when patients were under analgo-sedation for > 96 h or CV was suspected due to elevated transcranial doppler (TCD) values according to our standard operating procedures [29]. The last transcranial doppler (TCD) value before vasopressin administration was recorded to check for CV.

Patients received volume and catecholamine therapy according to standard recommendations and in dependance on the occurrence of cerebral vasospasm. The goal was to keep CPP > 70 mmHg [5]. The TBI

patient was treated according to the Brain Trauma Foundation guidelines [30] and actual literature [3]. During the ICU stay each of those patients suffered from at least one episode of refractory hypotension that could not be treated sufficiently by volume, hydrocortisone and catecholamines.

Therapeutical Intervention und CBF monitoring:

When the decision to try AVP was made a 3 I.U. bolus was applied and the effect on MAP, ICP and CPP was monitored. The goal was to establish a CPP > 70 mmHg. Since it was a preliminary study, we decided to measure CBF non-invasively using the Quantix ND® device.

The Quantix ND® (Cardiosonix Ltd, Israel) uses an angle-independent doppler technique that employs two ultrasound heads placed in a defined angle to each other in one insonation probe (Fig. 1), projecting actual flow diagrams on a real time monitor. Probe was placed in the submandibular region of a supine positioned patient and internal carotid artery (ICA) was located by identifying its specific flow diagram on the real time monitor. On the real-time monitor the volume flow, both angles (θ1,θ2), the measured diameters of the vessel (D1, D2), both measured velocities as to the laminar flow (L1,L2) and finally the shear force were monitored (Fig. 1). This information is continuously stored on the computer and can be later replayed for offline reevaluation. The system was evaluated at our clinic comparing CBF values measured by the QuantixND® compared with rCBF values [31–35]. We measured the flow volume in the internal carotid artery (ICA) since it was shown that the flow volume has an almost linear correlation with the cerebral blood flow on the measured side [31] but showed an even better correlation when flow volume in both ICA was measured and compared to global CBF [31].

When decision to use vasopressin in a patient was made, in all SAH patients the last transcranial doppler value was noted and the Quantix ND® was used to establish the baseline flow volume and thus the CBF before vasopressin administration. Additional measurements were performed 2, 10 and 20 minutes after vasopressin. In addition, MAP, ICP, and CPP was documented at the same timepoints. Patient outcome was evaluated at hospital discharge using the Glasgow Outcome Score (GOS). GOS 0 represents death, GOS 1–3 poor outcome and GOS 4–5 favorable outcome.

Results

Between 2014 and 2018 seven patients fulfilled the criteria for using vasopressin to treat hypotension refractory to fluid, norepinephrine, and hydrocortisone. One patient was treated for TBI, six patients were treated for aSAH four of whom developed cerebral vasospasm. All but one patient received a bolus of 3 I.JU. vasopressin, in patient 2 another bolus of 5 I.U. was needed to improve MAP. The outcome using the GOS was favorable in 2 patients, 3 patients were in the poor outcome group at time of hospital discharge (GOS3), both improved to GOS 4 after rehabilitation. Two patients died during hospital stay due to multi-infarct syndrome as sequelae of CV (for patient demographics see table 1).

In all examined patients robust external flow values in the internal carotid artery (ICA) values could be gathered before and 2, 10 and 20 minutes after vasopressin administration according to the standard

evaluations of the Quantix ND® device. For detailed values of each measurement and each patient see table 2–8. Elevation of MAP combined with reduction in ICP and thus elevated CPP could be achieved within 2 minutes after AVP administration and was still valid 10 and 20 minutes after AVP bolus. Mean MAP before vasopressin was 56,51 mmHg (± 4,5 mmHg) and CPP was 40,14 mmHg (± 8,86; 6,86). The mean increase in all patients over the examined timepoints was 37,39 mmHg and 40,19 mmHg respectively. This increase in MAP and CPP was neither paralleled in an increase in blood flow volume nor $P_{bt}O_2$. Blood flow volume was decreased in 5 of the aSAH patients, especially in those with signs of CV. In the one patient with normal TCD values blood flow volume stayed within the normal error of measurement. The mean blood flow in both carotid arteries was 320,30 ml/min before vasopressin administration and the overall mean reduction was 23,45 ml/min. In patients with signs of CV at time of vasopressin administration (patient 1,3 and 4) the mean blood flow volume was 286,83 ml/min and decreased to a mean flow volume of 241,42 ml/min. In contrast, the TBI patient showed an increase of MAP and CPP following vasopressin which was accompanied by an increase in blood flow volume. Thus, decision was made to continue AVP administration continuously (0,03 I.U./min) for 12 h to preserve a CPP > 65 mmHg (for details see table 6). Unfortunately, no $P_{bt}O_2$ probe was in place since this was not standard monitoring in TBI patients Patient was discharged after 23 days with good outcome.

$P_{bt}O_2$ in all patients measured showed no significant change except for patient 2 who had no signs of vasospasm and brain oxygenation improved slightly following vasopressin.

Discussion

In the present preliminary retrospective study, we found that administration of vasopressin does improve MAP and CPP in neurocritical care patients suffering from norepinephrine-refractory hypotension but failed to improve CBF, especially in patients with already compromised cerebral perfusion.

Due to the mostly independently regulated pathways of the different AVP receptors, synthetic agonists of the AVP receptors are routinely used in modern medicine, e.g. desmopressin, a V2 receptor agonist is used in diagnostics and treatment of diabetes insipidus or used for treatment of different coagulopathies such as von Willebrand disease [32] or to counteract effects of acetyl salicylic acid [33]. The AVPR1a- agonist vasopressin (AVP) or terlipressin are used in postoperative bowel distention, refractory hypotension after cardiac surgery [34] or to treat intraoperative hypotension or treatment of portal hypertension [35]. AVP experienced a renaissance for treatment of hypovolemic [36] or septic shock, refractory hypotension or in resuscitation [16,37]. The finely tuned and independent work mechanisms of AVP on its different receptors make it the ideal drug for treatment of patients after cardiac surgery suffering from low systemic resistance concomitant with pulmonary hypertension since it elevates systemic resistance while parallel decreasing pulmonary hypertension [38].

Those different work mechanisms make AVP a possible target for use in neurosurgical patients. Despite the fact that AVP can enhance cerebral edema after ischemia [25,39] and also leads to an increased

rebleeding rate in an animal model of SAH [40], some studies demonstrated that AVP is safe to use after TBI using the increase in MAP and CPP as endpoints [28,41], or in an animal model where cerebral oxygenation was also studied [27]. But to our knowledge this preliminary study is the first to measure not only the changes in MAP and CPP but put the focus of attention to changes in cerebral blood flow (CBF) after AVP administration. In the small number of patients included in our study we could clearly demonstrate a significant rise in MAP and CPP after administration of 3 I.U. AVP. Taken this as endpoint it would appear AVP is a safe to use alternative vasopressor in neurosurgical patients, especially after TBI and aSAH, giving the wanted results of an increased CPP. But the problem is the AVPR1a mediated contraction of smooth muscle cells that appears to happen also in cerebral vessels, reflected by the decrease or the lack of sufficient increase in CBF after AVP administration in our patients. This stands in contrast to norepinephrine which elevates systemic blood pressure without normally effecting cerebral vessels, making it the ideal catecholamine for aSAH patients.

Those findings and our data rise two questions: first - is CPP alone really the ideal target for treatment guidance in TBI and aSAH patients and second- is vasopressin safe to use in those patients?

The maintenance of sufficient MAP is important in all ICU patients but for neurosurgical patients after SAH or TBI it is essential to avoid delayed ischemia. So far, most neuro ICUs use MAP, ICP and CPP to guide their therapy for those patients. This still is considered sufficient, at least in TBI patients according to the Brain Trauma Foundation guidelines, but those simple treatment algorithms are nowadays challenged [42,43]. After TBI a dysfunction in cerebral autoregulation might occur [44], and the microcirculation seems to be dysregulated leading to distended arterioles [45] and thus more intracerebral blood volume. As consequence ICP can be elevated. Several studies concluded that a dynamic CPP concept depending on each patient's cerebrovascular autoregulatory capacities should be followed in ICU care after TBI [43,46]. Depreitere *et al*. also concluded that CPP alone is not sufficient for patient treatment and added the pressure reactivity index (PRx) defined by Czosnyka [47] to their monitoring. While current evidence regarding the use of $P_{bt}O_2$ remains promising [48] but mixed, three ongoing clinical multicenter trials are expected to definitively answer the question of what role $P_{bt}O_2$ monitoring plays in severe TBI (BOOST III, BONANZAand OXY-TC) [49].

In our neurosurgical ICU additional neuromonitoring ($P_{bt}O_2$ and/or CBF) is used in addition to ICP and CPP to steer therapy after TBI since 2021 and aSAH since 2014. But this is no standard at all since there exists no level I evidence so far that even an ICP/CPP guided therapy has any beneficial effects on patient outcome after TBI [50]. The findings of Van Harren et al. 2013 suggest that the disturbances in normal autoregulation especially in peripheral arterioles and brain function after TBI are complex and may take effect on various levels [28]. The influence of vasopressin on oxytocin receptors leading to vasodilation [13,16] are overridden on a dose dependent manner by vasopressin related activation of AVPR1a and thus vasoconstriction. This might be the reason for the beneficial effect of vasopressin after TBI seen by Van Harren 2013 and Dudkiewicz 2008. The AVPR1a activation led to elevation in MAP and due to constriction of small cerebral vessels to lower intracranial blood volume and thus lower ICP. This

was reflected in the results of the TBI patient in our own study. The AVP administration led to significant rise in MAP, lower ICP value and therefore increased CPP. From the concomitant elevation in CBF we conclude that AVP can at least partly counteract the autoregulatory dysfunction and optimize CPP and CBF without impairment of CBF. Thus, AVP seems to be safe to use for treatment of refractory hypotension in TBI patients. It might be even more beneficial than other vasopressors due to its potential effects on small cerebral vessels. Norepinephrine can only reduce ICP when autoregulation is intact, since it has no direct influence on cerebral vessels due to lack of passages through the blood brain barrier [51]. Hence the application of low dose AVP might be superior to catecholamines for ICU treatment of TBI patients regarding ICP and CPP management when signs of disturbed autoregulation are present. This hypothesis is supported by the findings of Dudkiewicz and Proctor in 2008 who could demonstrate that AVP maintained CPP but improved ICP and cerebral tissue oxygenation better that phenylephrine [27]. In addition, there is a new multicenter trial using a drug targeting the disturbed autoregulatory functions of small distended cerebral arterioles. Administration of the test drug ought to lead to small vessel contraction thus lowering ICP.

The use of CPP as therapy guidance in patients with SAH is a completely different story. Depending on the severity of the initial bleeding patients can be awake and neurologically assessable or are analgo-sedated and on a ventilator for extended time periods. Cerebral vasospasm is still the major cause for mortality and morbidity after SAH. Vasospasm leads to a decrease in vascular diameter hence an increase in cerebrovascular resistance. The decreased blood flow is often followed by delayed cerebral ischemia leading to catastrophic neurological outcomes or even death [52]. The use of CPP as therapy guidance after SAH is problematic because one can only roughly estimate CBF since it doesn't take vessel diameter, resistance, or blood viscosity into account [53]. But increased vascular resistance plays the key role in CBF after SAH. It is suggested to use at least brain oxygen measurements to avoid DCI due to non-optimal CPP or CBF [54]. It has been shown that $P_{bt}O_2$ values can help to find the optimal CPP since patients with aSAH are at risk for insufficient CBF if CPP_{opt} is not reached and might develop DCI [55]

We suggest that multimodal neuromonitoring measuring $P_{bt}O_2$ (Licox® or the Raumedic® PTO probe and if available CBF monitoring (Hemedex probe) should be used in addition to ICP/CPP measurement to optimize ICU treatment and to determine the needed MAP and CPP for each patient individually. This could save volume load and catecholamine administration since the ideal MAP level for each patient could be set (ranges often between 70–140 mmHg). In aSAH we use $P_{bt}O_2$ and CBF monitoring regularly and have good outcome results (unpublished data and [29]) but so far, no level I evidence exists showing that the use of additional neuromonitoring has a significant influence on patient outcome [6]. This is not due to lack of studies but due to the intraindividual variability of patients' needs and therefore difficulties in finding standardized treatments settings that are used in equally in all participating clinics.

The maintenance of a sufficient CPP according to dependent variables as $P_{bt}O_2$ and CBF is normally done using hypertension therapy [4]. In cases when norepinephrine-refractory hypotension occurs, AVP could again be the drug of choice due to its vasoconstrictive effects. But our data clearly demonstrated

that the increased MAP combined with decreased ICP leading to elevated CPP was not accompanied by a concomitant improvement of CBF in SAH patients. In addition, we did not see any improvement in $P_{bt}O_2$ value in patients following vasopressin administration. This effect was especially seen in patients with elevated TCD velocities suggestive of cerebral vasospasm. This might be due to the dose dependent effects of AVP. The bolus administration of 3 I.U. vasopressin possibly leads to the stimulation of AVPR1a overriding the potential beneficial effects of oxytocin receptor stimulation and increased NO release in the brain. The possible modulation of NO release and thus vasodilation could be a very useful tool for prevention of severe cerebral vasospasm after SAH. New studies allude to the fact that cerebral vasospasm is not exclusively a disease of the larger vessels but might occur at early stages mainly in microcirculation. Terpolilli et al. showed promising data using NO-ventilation to prevent microcirculatory vasospasm after SAH (presentation at the 2014 annual DGNC meeting). Since AVP can also modulate and release NO, it could be useful at early timepoints after SAH to avoid occurrence of vasospastic events in microcirculation. But further studies must be done to exploit this possibility. So far, om our preliminary data show that AVP can counteract refractory hypotension in SAH patients but does not lead to sufficient improvement of CBF. In contrast, in three patients CBF was even decreased after AVP administration despite significantly increased CPP, pointing out that AVP possibly exerts a vasoconstrictive effect on cerebral blood vessels. That suggests that despite the beneficial effect on refractory hypotension AVP should be used with retentiveness in patients with impaired cerebral perfusion but further studies using continuous invasive CBF monitoring, and more patients need to be done to finally decide the fate of AVP in those patients.

Conclusion

Vasopressin is an alternative vasopressor for treatment of refractory hypotension to avoid organ hypoperfusion in ICU patients. It seems practicable for TBI patients, but our preliminary data showed that in general it should be used with care in neurosurgical patients, especially when cerebral blood flow might be compromised e.g. by cerebral vasospasm since it does neither improved CBF nor $P_{bt}O_2$ values. When using vasopressin in those patients, CBF or at least $P_{bt}O_2$ should be monitored to evaluate if the increase in CPP in accompanied by an increase in brain oxygenation to avoid cerebral ischemia. But studies with larger patient groups measuring cerebral tissue oxygenation and CBF by using intraparenchymal probes like the QFlow 500™ by Hemedex, Waldham USA® should be carried out to support these findings.

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Tables

Table 1 shows the relevant demographic data of the included patients. AL= aneurysm location, ACoA= anterior cerebral artery, GCS= Glasgow Coma Score, GOS= Glasgow Outcome Scale, MCA= middle cerebral artery, n= no, na= not applicable, SAH= Subarachnoid Hemorrhage, TBI= Traumatic Brain Injury, y= yes, WFNS World Federation of Neurosurgeons Score

Table 1 Demographic data

	gender	age	diagnosis	WFNS	GCS	AL	vasospasm	GOS
Patient 1	**f**	**57**	**SAH**	**2**	**13**	**MCA**	**y**	**0**
Patient 2	**m**	**43**	**SAH**	**4**	**8**	**ACoA**	**n**	**4**
Patient 3	**f**	**48**	**SAH**	**3**	**11**	**MCA**	**y**	**3**
Patient 4	**m**	**61**	**SAH**	**1**	**15**	**ACoA**	**y**	**0**
Patient 5	**m**	**40**	**TBI**	**na**	**7**	**na**	**na**	**4**
Patient 6	**f**	**42**	**SAH**	**3**	**9**	**MCA**	**y**	**3**
Patient 7	**f**	**58**	**SAH**	**2**	**13**	**ACoA**	**n**	**4**

Table 2 shows all relevant measurements for patient 1 before (timepoint 1) and at the 3 timepoints after vasopressin. Timepoint 2 representing 2 minutes, timepoint 3=10 minutes and timepoint 4= 20 minutes following vasopressin administration.

Table 2 Detailed measurement data Patient 1

					Quantix ml/min		TCD cm/sec	
Timepoints	MAP	ICP	CPP	PbtO2	ACI l	ACI r	LMCA	RMCA
1	56	12	44	22	289	276	217	198
2	94	10	84	18	216	229		
3	92	15	77	16	208	213		
4	86	15	71	18	220	228		
Mean	90,67	13,33	77,33	17,33	214,67	223,33		

ACI l= left internal carotid artery, ACI r = right internal carotid artery, CPP=cerebral perfusion pressure in mmHg, ICP= intracranial pressure in mmHg, LMCA= left middle cerebral artery, MAP= mean arterial pressure in mmHg, $P_{bt}O_2$=brain tissue oxygenation in mmHg, Quantix = blood flow volume in ml/min, RMCA= right middle cerebral artery, TCD= transcranial doppler in cm/sec

Table 3 shows all relevant measurements for patient 2 before (timepoint 1) and at the 3 timepoints after vasopressin. Timepoint 2 representing 2 minutes, timepoint 3=10 minutes and timepoint 4= 20 minutes following vasopressin administration.

Table 3 Detailed measurement data Patient 2

					Quantix ml/min		TCD cm/sec	
Timepoints	MAP	ICP	CPP	PbtO2	ACI l	ACIr	LMCA	RMCA
1	52	15	37	16	354	339	132	128
2	87	12	75	22	330	316		
3	90	14	76	24	358	342		
4	88	14	74	22	350	347		
Mean	88,33	13,33	75,00	21,00	346,00	335,00		

ACI l= left internal carotid artery, ACI r = right internal carotid artery, CPP=cerebral perfusion pressure in mmHg, ICP= intracranial pressure in mmHg, LMCA= left middle cerebral artery, MAP= mean arterial pressure in mmHg, $P_{bt}O_2$=brain tissue oxygenation in mmHg, Quantix = blood flow volume in ml/min, RMCA= right middle cerebral artery, TCD= transcranial doppler in cm/sec

Table 4 shows all relevant measurements for patient 3 before (timepoint 1) and at the 3 timepoints after vasopressin. Timepoint 2 representing 2 minutes, timepoint 3=10 minutes and timepoint 4= 20 minutes following vasopressin administration. ACI l= left internal carotid artery, ACI r = right internal carotid artery, CPP=cerebral perfusion pressure in mmHg, ICP= intracranial pressure in mmHg, LMCA= left middle cerebral artery, MAP= mean arterial pressure in mmHg, $P_{bt}O_2$=brain tissue oxygenation in mmHg, Quantix = blood flow volume in ml/min, RMCA= right middle cerebral artery, TCD= transcranial doppler in cm/sec

Table 4 Detailed measurement data Patient 3

					Quantix ml/min		TCD cm/sec	
Timepoints	MAP	ICP	CPP	PbtO2	ACI l	ACIr	LMCA	RMCA
1	60	20	40	21	289	276	210	188
2	87	16	82	16	216	229		
3	94	15	79	18	258	232		
4	90	15	75	20	278	266		
Mean	90,33	15,33	78,67	18,00	250,67	242,33		

Table 5 shows all relevant measurements for patient 4 before (timepoint 1) and at the 3 timepoints after vasopressin. Timepoint 2 representing 2 minutes, timepoint 3=10 minutes and timepoint 4= 20 minutes following vasopressin administration. ACI l= left internal carotid artery, ACI r = right internal carotid artery, CPP=cerebral perfusion pressure in mmHg, ICP= intracranial pressure in mmHg, LMCA= left middle cerebral artery, MAP= mean arterial pressure in mmHg, n.a.= not applicable, $P_{bt}O_2$=brain tissue oxygenation in mmHg, Quantix = blood flow volume in ml/min, RMCA= right middle cerebral artery, TCD= transcranial doppler in cm/sec

Table 5 Detailed measurement data Patient 4

					Quantix ml/min		TCD cm/sec	
Timepoints	MAP	ICP	CPP	PbtO2	ACI l	ACIr	LMCA	RMCA
1	61	17	44	14	326	265	165	176
2	108	14	94	15	302	246		
3	106	15	91	14	288	230		
4	96	14	82	16	264	228		
Mean	103,33	14,33	89,00	15,00	284,67	234,67		

Table 6 shows all relevant measurements for patient 5 before (timepoint 1) and at the 3 timepoints after vasopressin. Timepoint 2 representing 2 minutes, timepoint 3=10 minutes and timepoint 4= 20 minutes following vasopressin administration. ACI l= left internal carotid artery, ACI r = right internal carotid artery, CPP=cerebral perfusion pressure in mmHg, ICP= intracranial pressure in mmHg, LMCA= left middle cerebral artery, MAP= mean arterial pressure in mmHg, $P_{bt}O_2$=brain tissue oxygenation in mmHg, Quantix = blood flow volume in ml/min, RMCA= right middle cerebral artery, TCD= transcranial doppler in cm/sec

Table 6 Detailed measurement data Patient 5

					Quantix ml/min		TCD cm/sec	
Timepoints	MAP	ICP	CPP	PbtO2	ACI l	ACIr	LMCA	RMCA
1	52	18	34	n.a.	387	341	n.a.	n.a.
2	99	13	86	n.a.	442	386		
3	98	12	86	n.a.	428	392		
4	89	12	77	n.a.	402	366		
Mean	95,33	12,33	83,00		424,00	381,33		

Table 7 shows all relevant measurements for patient 6 before (timepoint 1) and at the 3 timepoints after vasopressin. Timepoint 2 representing 2 minutes, timepoint 3=10 minutes and timepoint 4= 20 minutes following vasopressin administration. ACI l= left internal carotid artery, ACI r = right internal carotid artery, CPP=cerebral perfusion pressure in mmHg, ICP= intracranial pressure in mmHg, LMCA= left middle cerebral artery, MAP= mean arterial pressure in mmHg, $P_{bt}O_2$=brain tissue oxygenation in mmHg, Quantix = blood flow volume in ml/min, RMCA= right middle cerebral artery, TCD= transcranial doppler in cm/sec

Table 7 Detailed measurement data Patient 6

					Quantix ml/min		TCD cm/sec	
Timepoints	MAP	ICP	CPP	PbtO2	ACI l	ACIr	LMCA	RMCA
1	60	20	49	15	312	310	172	130
2	92	17	75	17	308	312		
3	100	15	85	17	310	298		
4	92	16	76	16	308	366		
Mean	94,67	16,00	78,67	16,67	308,67	325,33		

Table 8 shows all relevant measurements for patient 7 before (timepoint 1) and at the 3 timepoints after vasopressin. Timepoint 2 representing 2 minutes, timepoint 3=10 minutes and timepoint 4= 20 minutes following vasopressin administration. ACI l= left internal carotid artery, ACI r = right internal carotid artery, CPP=cerebral perfusion pressure in mmHg, ICP= intracranial pressure in mmHg, LMCA= left middle

cerebral artery, MAP= mean arterial pressure in mmHg, $P_{bt}O_2$=brain tissue oxygenation in mmHg, Quantix = blood flow volume in ml/min, RMCA= right middle cerebral artery, TCD= transcranial doppler in cm/sec

Table 8 Detailed measurement data Patient 7

					Quantix ml/min		TCD cm/sec	
Timepoints	MAP	ICP	CPP	PbtO2	ACI l	ACIr	LMCA	RMCA
1	55	22	33	12	402	328	143	165
2	96	17	79	15	387	324		
3	98	15	83	15	390	298		
4	96	16	80	14	394	300		
Mean	96,67	16,00	80,67	14,67	390,33	307,33		

Figures

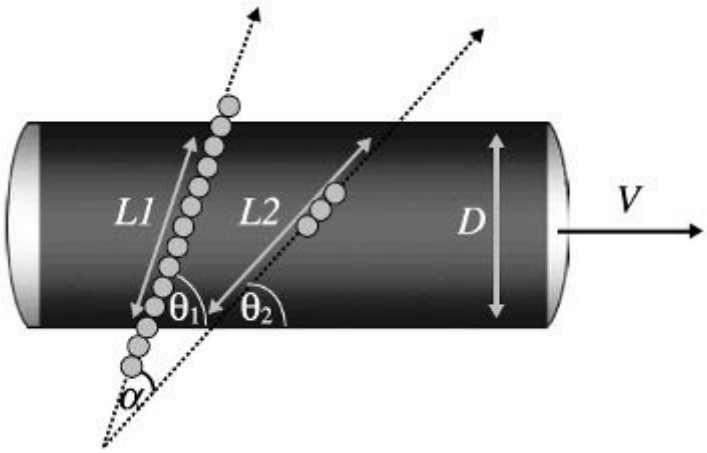

Figure 1

Shows a schematic of the ICA using the Quantix ND® System with L1 representing the laminar flow beam 1, L2 the laminar flow beam 2. D represents the vessel diameter, V the volume and α the insonated angle to measure total flow volume within the carotid artery.