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ORIGINAL ARTICLE

Cerebral autoregulation after aneurysmal subarachnoid haemorrhage. A preliminary study comparing dexmedetomidine to propofol and/or midazolam

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Background: Cerebral autoregulation is often impaired after aneurysmal subarachnoid haemorrhage (aSAH). Dexmedetomidine is being increasingly used, but its effects on cerebral autoregulation in patients with aSAH have not been studied before. Dexmedetomidine could be a useful sedative in patients with aSAH as it enables neurological assessment during the infusion. The aim of this preliminary study was to compare the effects of dexmedetomidine on dynamic and static cerebral autoregulation with propofol and/or midazolam in patients with aSAH.

Methods: Ten patients were recruited. Dynamic and static cerebral autoregulation were assessed using transcranial Doppler ultrasound during propofol and/or midazolam infusion and then during three increasing doses of dexmedetomidine infusion (0.7, 1.0 and 1.4 μg/kg/h). Transient hyperaemic response ratio (THRR) and strength of autoregulation (SA) were calculated to assess dynamic cerebral autoregulation. Static rate of autoregulation (sRoR)% was calculated by using noradrenaline infusion to increase the mean arterial pressure 20 mm Hg above the baseline.

Results: Data from nine patients were analysed. Compared to baseline, we found no statistically significant changes in THRR or sROR%. THRR was (mean ± SD) 1.20 ± 0.14, 1.17 ± 0.13 ($P = .93$), 1.14 ± 0.09 ($P = .72$) and 1.19 ± 0.18 ($P = 1.0$) and sROR% was 150.89 ± 84.37, 75.22 ± 27.75 ($P = .08$), 128.25 ± 58.35 ($P = .84$) and 104.82 ± 36.92 ($P = .42$) at baseline and during 0.7, 1.0 and 1.4 μg/kg/h dexmedetomidine infusion, respectively. Dynamic SA was significantly reduced after 1.0 μg/kg/h dexmedetomidine ($P = .02$).

Conclusions: Compared to propofol and/or midazolam, dexmedetomidine did not alter static cerebral autoregulation in aSAH patients, whereas a significant change was observed in dynamic SA. Further and larger studies with dexmedetomidine in aSAH patients are warranted.

1 | INTRODUCTION

Aneurysmal subarachnoid haemorrhage (aSAH) is a detrimental disease often affecting a relatively young population and leading to severe disability. Cerebral autoregulation maintains the cerebral blood flow constant despite changes in mean arterial pressure by changing cerebrovascular resistance. Dynamic and static autoregulation reflect rapid responses to changes in pressure pulsation and slow responses to changes in mean arterial pressure, respectively.[1] Previous studies have reported that impaired cerebral autoregulation in patients with aSAH predicts the development of radiological vasospasm and delayed cerebral ischemia (DCI); and may correlate with poor outcome.[2-4]

Dexmedetomidine is a selective α_2-agonist which induces sedation, anxiolysis and analgesia with minimal respiratory depression. Importantly, it allows patient awakening despite uninterrupted infusion enabling frequent neurological evaluation.[5] These properties and potential neuroprotective effects make dexmedetomidine desirable in neurocritical care.[6] While dexmedetomidine seems to attenuate dynamic cerebral autoregulation in healthy volunteers,[7] its effects on cerebral autoregulation in aSAH patients are unknown. Thus, the primary aim of this preliminary study was to compare dynamic and static cerebral autoregulation in patients with aSAH under dexmedetomidine vs propofol and/or midazolam sedation. We did not aim to study the effect of aSAH on autoregulation per se.

Editorial Comment

There may be concern for effects of potent vasodilatory drugs on cerebral vascular tone and responsiveness in patients with intracranial injury. The authors report here that cerebral blood flow autoregulation was unchanged in post-aneurysmal subarachnoid haemorrhage patients who were sedated with dexmedetomidine compared to sedation with midazolam or propofol.

2 | METHODS

The study was conducted in the Intensive Care Unit in Turku University Hospital, Turku, Finland. The study protocol (EudraCT 2012-000068-11, ClinicalTrials.gov identifier NCT01664520) conformed to the revised Declaration of Helsinki[8] and was approved by the ethical review board of the Hospital District of Southwest Finland (31/180/2012) and by the Finnish National Agency for Medicines. Written informed consent was obtained from the next of kin.

Patients aged 18-80 years suffering from aSAH and requiring sedation and mechanical ventilation after aneurysmal treatment (coiling or clipping) were included. aSAH patients not requiring sedation or mechanical ventilation were excluded. Other exclusion criteria were pregnancy, nursing women, sick sinus syndrome, carotid stenosis, heart rate <50 beats/min, mean arterial pressure <55 mm Hg, baseline middle cerebral artery (MCA) flow velocity (V_{MCA}) ≥120 cm/s suggesting vasospasm and clinical signs of DCI.

All patients received intravenous nimodipine infusion and were treated according to Neurocritical Care Society recommendations with local modifications.[9] ICP was measured continuously using intraparenchymal sensors, either Neurovent-PTO (Raumedic AG, Helmbrechts, Germany) or Codman® ICP Monitoring system (DePuy Synthes, Wokingham, UK). Neurovent-PTO was used in seven patients whereas Codman was used in one patient. Of the eight patients with intraparenchymal ICP catheter, four patients also had an external ventricular drainage (EVD) due to hydrocephalus. Two patients had only EVD and in those patients, cerebrospinal fluid was continuously drained and ICP was measured periodically. Cerebral oxygenation was monitored continuously using bilateral near-infrared spectroscopy (NIRS) with INVOS™ cerebral oximetry. In patients with Neurovent-PTO, brain tissue oxygenation ($PtiO_2$) was also monitored. Transcranial Doppler (TCD) was used to measure bilateral V_{MCA} using 2 MHz-probes (Atys, Soucieu-en-Jarrest, France) fixed with a head frame.

2.1 | Study protocol

First, static and dynamic autoregulation were assessed during a constant rate of propofol (2-5 mg/kg/h) and/or midazolam infusion (0.03-0.3 mg/kg/h) (baseline). Thereafter propofol and/or midazolam infusion was stopped and dexmedetomidine (Dexdor® Orion Oyj, Helsinki, Finland) infusion was commenced at a dose of 0.7 μg/

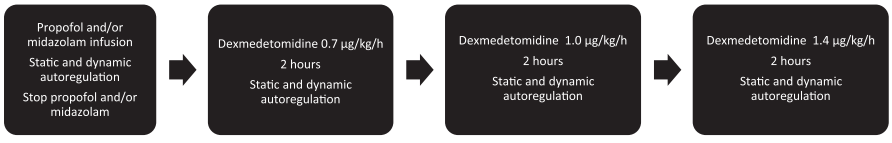

FIGURE 1 Study protocol

kg/h according to the total body weight. After two hours of dexmedetomidine infusion at constant rate (in order to reach a steady state), static and dynamic autoregulation were assessed again. While obtaining the steady dexmedetomidine state, all patients received 1-3 mg intravenous doses of oxycodone for analgesia at the discretion of the ICU nurse treating the patient. Next, dexmedetomidine infusion was increased to 1 μg/kg/h for two hours following which, static and dynamic autoregulation were assessed. Finally, dexmedetomidine dose was increased to 1.4 μg/kg/h for another two hours and autoregulation tests were performed once again (see Figure 1). After each period of two hours of dexmedetomidine infusion, arterial blood was sampled to measure the plasma dexmedetomidine concentration (details in supplementary material). During the autoregulation tests, no opioids or other drugs were administered. No blinding was performed. To avoid the effects of temperature, haemoglobin (Hb) and ventilation on cerebral blood flow velocity, these variables were kept constant throughout the study.

2.2 | Dynamic autoregulation test

Dynamic autoregulation was assessed with transient hyperaemic response test (TORT) which is considered safe during the acute phase of SAY.[10-12] The common carotid artery was compressed for eight seconds while the ipsilateral MCA flow velocity (FV) was recorded before and after releasing compression. Two investigators were always present during the assessment; the compression of carotid artery was performed by the same investigator in all cases (MK) and the FV readings were manually recorded either by RT, MR, JP or AK. The adequacy of compression was assessed visually (a sudden decrease in V_{MCA} with no further decrease). The test was accepted only when the haemodynamic parameters remained stable during the compression. The intervention was discontinued if there was sinus arrest or if intracranial pressure (ICP) increased above 20 mm Hg. When the carotid artery is compressed, a drop in perfusion pressure leads to distal cerebrovascular dilatation as a compensatory mechanism if autoregulatory mechanisms are active. Consequently, after releasing the compression, the V_{MCA} increases beyond the pre-compression value leading to hyperaemic response. However, in case of impaired autoregulation, no cerebrovascular dilatation or transient hyperaemia will occur.

Transient hyperaemic response ratio (THRR) was calculated as previously described.[11]

$$\text{THRR} = \frac{\text{systolic FV}_{\text{hyperaemia}}}{\text{systolic FV}_{\text{baseline}}}$$

The baseline FV was systolic FV before compression. Due to overshoot phenomenon, the first cardiac cycle was ignored and the systolic $FV_{hyperaemia}$ was the average of the systolic FV of the second and third cardiac cycles after the compression.[11]THRR was repeated three times on both hemispheres and there was at least 60 seconds interval between the measurements. The data were averaged from both hemispheres[13] and considered normal if THRR was ≥1.09 and impaired if THRR was <1.09.[10]

Strength of dynamic autoregulation (SA) was calculated as

$$\text{SA} = \frac{\text{systolic FV}_{\text{hyperaemia}} \times \text{MAP of 60 mm Hg}}{\text{MAP} \times \text{systolic FV}_{\text{baseline}}}$$

where systolic $FV_{hyperaemia}$ is the first flow velocity after the release of carotid compression and MAP of 60 mm Hg represents the lower limit of autoregulation. MAP is the mean arterial pressure immediately before the THRT and $FV_{baseline}$ is the flow velocity before carotid compression.[14] SA value <1 suggests under regulation and >1 hyperregulation.[15] In the underregulated situation, cerebral blood vessels are already dilated and a decrease in blood pressure does not result in further dilation, whereas in hyperregulation the cerebral blood vessels dilate more than should be necessary.[15]

2.3 | Static autoregulation test

Static autoregulation was tested by increasing the mean arterial pressure (MAP) by 20 mm Hg with noradrenaline infusion while V_{MCA} was continuously monitored with TCD. After the MAP had reached the desired level, the final V_{MCA} was considered to be mean of the 20 min $V_{MCA.}$[16]

Measured MAP and FV were used to calculate estimated cerebral vascular resistance (CVRe):

$$\text{CVRe} = \frac{\text{MAP}}{\text{FV}}$$

If the percentage change of CVR equals to percentage change in MAP, there would be no change in FV, indicating intact autoregulation.

Static rate of autoregulation (sRoR)% describes the change in cerebrovascular resistance (CVR) determined from the relation between cerebral blood flow velocity (CBFV) and changing cerebral perfusion pressure (CPP). It is calculated:

$$\text{sRoR\%} = (\Delta\text{CVR\%}/\Delta\text{CPP\%}) \times 100, \text{ where CVR} = \text{CPP} \div \text{FV}.$$

However, in those patients who had only EVD, we used MAP (as the CSF was continuously drained) in the formula and sROR% was calculated:

$$\text{sRoR\%} = 100 \times (\text{Initial}V_{mca}/\text{Final}V_{mca}) - (\text{InitialMAP}/\text{FinalMAP}) \div 1 - (\text{InitialMAP}/\text{FinalMAP})$$

sRoR of 100% or more indicates that autoregulation is completely intact, meaning that cerebral blood flow velocity is independent of cerebral perfusion pressure.[17] sROR of 0% indicates that cerebral autoregulation is completely absent, and cerebral blood flow is linearly related to cerebral perfusion pressure. sROR of 50% is regarded as the cut-off for failure of autoregulation. Accordingly,

sRoR indicates quantitatively the stability of changes in cerebral blood flow when arterial blood pressure varies.[18]

2.4 | Statistical analysis

Data are presented as mean ± SD. All physiological and TCD parameters including autoregulation indices at various dexmedetomidine doses were compared to their respective baseline values recorded with propofol/midazolam. Power analysis was not performed, and our sample size was based on previous similar autoregulation studies using TCD measurements.[19-21] The initial aim was to recruit 15 patients, but the recruitment was unexpectedly difficult (due to refusals of next of kin or suspicion of vasospasms in TCD) and very slow (from year 2013 to 2017).

Repeated measures analysis of variance with Dunnett's adjustment for multiple comparisons was used to compare autoregulation indices at various dexmedetomidine doses to their respective baseline values (propofol/ midazolam). $P < .05$ was considered statistically significant. Statistical analyses were done using SAS 9.4 System for Windows (SAS Institute Inc, Cary, NC).

3 | RESULTS

Five male and five female patients with mean age of 58.4 ± 10.5 years were recruited. One patient was excluded from dynamic and static autoregulation tests as she had no temporal acoustic window for the TCD, leaving nine patients for the analysis. The demographic data for the patients is shown in Table 1.

Three patients had no temporal acoustic window on the left side and the Doppler measurements were done only on the right side. One patient expressed profound bradycardia during the dynamic test and was included only in the static test. As a baseline sedation, six patients had propofol infusion, two patients had midazolam infusion, one patient had midazolam infusion combined with propofol infusion and one patient did not have any sedation. The recruitment and the autoregulation tests took place during the first 24-48 hours after the surgical or endovascular treatment. The doses of oxycodone given to the patients between the measurements were 2.8 ± 1.5 mg after the commencement of the infusion of dexmedetomidine, 2.7 ± 1.9 mg after 1.0 μg/kg/h and 2.3 ± 1.4 mg after 1.4 μg/kg/h dexmedetomidine.

There was no significant difference between the Hb, PaO_2 and $PaCO_2$ values at each concentration of dexmedetomidine compared to baseline (Table 2). MAP and CPP were controlled with a noradrenaline-infusion.

Overall, the SA was significantly lower after the 1.0 μg/kg/h dose of dexmedetomidine compared to baseline (0.75 ± 0.05, $P = .02$) No other statistically significant difference was observed in THRR or SA (Figure 2, Table 3) with dexmedetomidine compared with propofol and/or midazolam. There was also no difference in the static parameters V_{MCA}, CVR, sROR% (Figure 3) and PI (Figure 4) with dexmedetomidine compared with propofol and/or midazolam (Table 4).

One patient had impaired dynamic autoregulation at baseline, and it did not change with the administration of dexmedetomidine.

TABLE 1 Demographics of the patients that were included in the analysis. Data is presented as mean ± SD

Age (y)	58.1 ± 11.1
Height (cm)	173.4 ± 8.2
Weight (kg)	74.8 ± 11.4
Sex (male/female*)	5/ 4
GCS at admission (grade)	(n)
15	1
13	1
12	2
9	1
6	1
5	1
3	2
Hunt & Hess (grade)	(n)
3	4
4	4
5	1
Fisher (grade)	(n)
3	2
4	7
Aneurysm	(n)
ICA (dx/sin)	3 (2/0)
MCA (dx/sin)	4 (2/2)
ACA	3
Treatment	(n)
Coiling	7
Coiling and stenting	0
Clipping	2
Study performed days after rupture	(n)
2	3
3	3
4	2
5	1
Smoking (yes/no/not known)	4/4/1
Hypertension (yes/no)	2/7
Diabetes (yes/no)	0/9

*The one excluded patient was female, 61 years old, had GCS 6 at admission, Fisher 4, Hunt & Hess 4, had ICA l.sin aneurysm that was treated with coils and stent three days after rupture,, she was a smoker and had diabetes and hypertension.

This patient had impaired THRR values bilaterally. One patient had an impaired dynamic autoregulation on THRT after the initial dose of dexmedetomidine, but not after higher doses. One patient had THRR < 1.08 after the initial and the 1.0 μg/kg/h dose, but not after the highest dose, and one other patient showed an impaired dynamic autoregulation after the two highest doses. SA values were < 1 in all patients, and there was a statistically significant reduction in SA after the 1.0 μg/kg/h dose compared to baseline ($P = .02$).

TABLE 2 $PaCO_2$ PaO_2 and Haemoglobin (Mean ± SD) at baseline and at different doses of dexmedetomidine (Dex). There were no statistically significant changes at different dexmedetomidine doses compared to baseline

	Propofol	Dex 0.7	*P*-value	Dex 1.0	*P*-value	Dex 1.4	*P*-value
$PaCO_2$ (mm Hg)	37.3 ± 2.3	36.2 ± 2.6	.62	35.4 ± 2.5	.21	35.0 ± 2.3	.10
PaO_2 (mm Hg)	132.4 ± 37.3	149.7 ± 57.7	.82	152.7 ± 59.1	.75	151.1 ± 62.2	.79
Hb (g/l)	124 ± 16	127 ± 15	.92	128 ± 14	.88	129 ± 14	.79

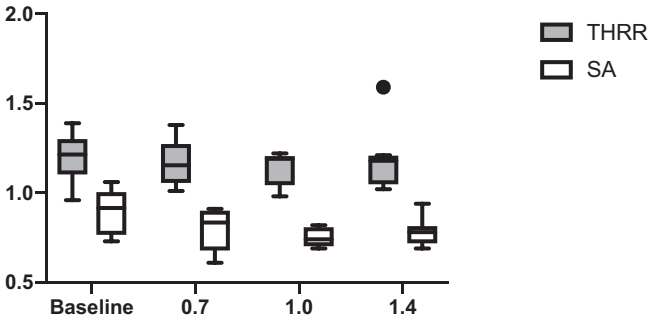

FIGURE 2 Boxplot for dynamic autoregulation indices, THRR and SA, at baseline (propofol/midazolam) and at each dose of dexmedetomidine. Boxes represent lower quartiles, medians and upper quartiles, whiskers represent 1.5 × inert-quartile ranges below and above the lower and upper quartiles, respectively. Outlying values are marked with a symbol

The patient, who had impaired dynamic autoregulation at baseline also had sROR% values < 50% throughout the study indicating impaired static autoregulation. Three other patients had sROR% < 50% at some point during the study.

There was no difference in cerebral oxygenation ($PtiO_2$ and NIRS, Table 4) between baseline and different doses of dexmedetomidine.

Figure 5 shows a Bland-Altman plot to compare the agreement of the sROR% measurements using MAP or CPP.

We performed a subgroup analysis of the data for the five patients who had TCD measurements from both sides. We found no statistical differences in the autoregulation indices at any dexmedetomidine dose compared to baseline (data not shown).

The cumulative dose of propofol before the commencement of dexmedetomidine was 6004 ± 4165 mg (N = 7) and that of midazolam was 125.7 ± 79 mg (N = 3). The mean dexmedetomidine concentrations were 0.7 ± 0.22 ng/mL (after 0.7 μg/kg/h for 2 hours), 1.19 ± 0.35 ng/mL (after 1.0 μg/kg/h for 2 hours) and 1.69 ± 0.39 ng/ml (after 1.4 μg/kg/h for 2 hours). There was a trend towards a lower noradrenaline requirement with increasing dose of dexmedetomidine, but we found no statistically significant difference between the noradrenaline doses.

4 | DISCUSSION

In this preliminary study, where each patient with aSAH served as their own control, dexmedetomidine did not change static cerebral autoregulation indices compared to propofol and/or midazolam. SA was significantly lower after 1.0 μg/kg/h dose of dexmedetomidine when compared to propofol and/or midazolam, although there were no significant changes in other dynamic autoregulation indices even with higher doses.

Cerebral autoregulation is often impaired in the first days after aSAH[19] and is associated with poor outcome.[3,4,20] Previous studies have primarily concentrated on the dynamic component of cerebral autoregulation in aSAH patients. To the best of our knowledge, only one study has evaluated static autoregulation in aSAH and found that it was not impaired.[21] No previous studies have evaluated both

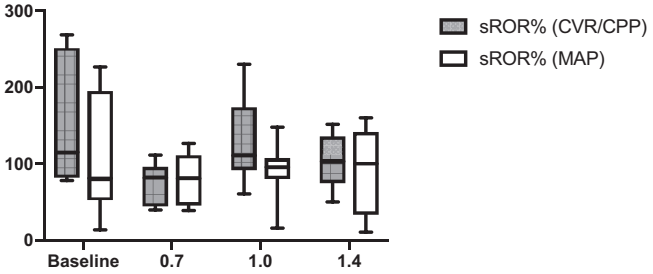

FIGURE 3 Boxplots for static rate of autoregulation, sROR%, calculated using MAP or CPP at baseline (propofol/midazolam) and at each dose of dexmedetomidine. Boxes represent lower quartiles, medians and upper quartiles, whiskers represent 1.5 × inert-quartile ranges below and above the lower and upper quartiles, respectively

TABLE 3 The indices for dynamic cerebral autoregulation at baseline (Propofol and/or Midazolam) and at different doses of dexmedetomidine (Dex)

	Baseline	Dex 0.7	*P*-value	Dex 1.0	*P*-value	Dex 1.4	*P*-value
THRR both	1.20 ± 0.14	1.17 ± 0.13	.93	1.14 ± 0.09	.72	1.19 ± 0.18	1.0
SA both	0.89 ± 0.13	0.80 ± 0.12	.15	0.75 ± 0.05	.02	0.78 ± 0.08	.07

Note: THRR, transient hyperemic response ratio; SA, strength of autoregulation.

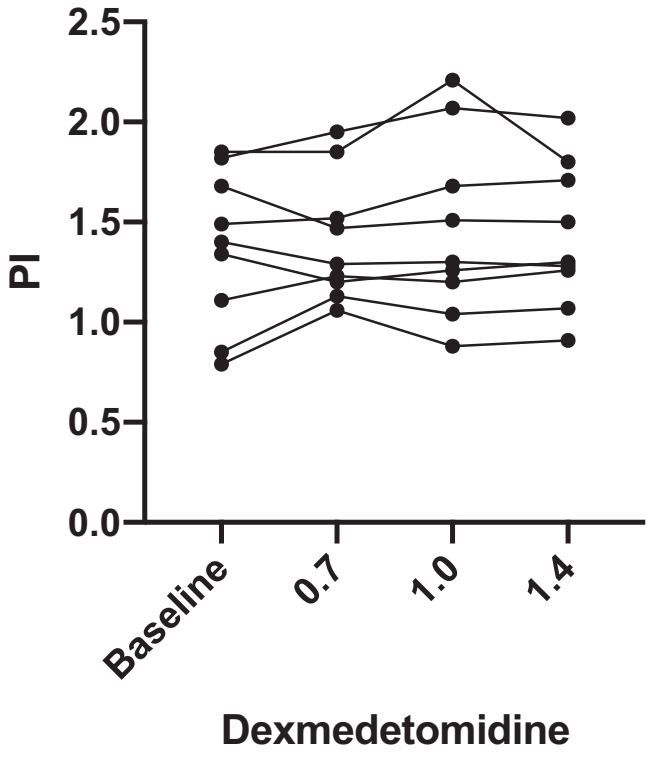

FIGURE 4 Individual values for pulsatility index, PI, at baseline (propofol/midazolam) and at each dose of dexmedetomidine

elements of autoregulation in aSAH patients. We decided to test both dynamic and static cerebral autoregulation because they may be differently affected. For example, in ischaemic stroke patients, while dynamic autoregulation is impaired for several days during the acute phase, static autoregulation remains unaffected.[22,23] Moreover, some anaesthetic agents impair dynamic but not static cerebral autoregulation.[24,25]

There are multiple methods for investigating cerebral autoregulation. These include examining the recovery of CBFV after a rapid decrease of arterial blood pressure by using thigh cuff test[26-28] and examining spontaneous fluctuations in CBFV in relationship with MAP, ICP and brain tissue oxygenation (Cambridge Enterprise Ltd, University of Cambridge, UK).[29] We used the THRT for assessing dynamic autoregulation because it allows brief period of reduction in CBFV and is deemed safe in aSAH. Furthermore, we calculated SA, which is not affected by hemodynamic factors.[15] Studying static cerebral autoregulation is traditionally performed by increasing MAP with a vasopressor and simultaneously measuring MAP and MCA flow velocities.[27] Modern techniques use PET scanning, which images CBF.[30] However, we preferred TCD to be able to perform the testing on the patient's bedside and to avoid the need to transport intubated and sedated patients for imaging.

In healthy, anaesthetised patients, there is a correlation between both dynamic autoregulation tests (thigh cuff test, THRT and

TABLE 4 The indices for static cerebral autoregulation at baseline (Propofol and/or Midazolam) and at different doses of dexmedetomidine (Dex); initial states the baseline values before the augmentation of MAP and final states the values during increased MAP

	Baseline	Dex 0.7	*P*-value	Dex 1.0	*P*-value	Dex 1.4	*P*-value
MAP mm Hg initial	80.70 ± 10.51	87.50 ± 9.0	.22	88.90 ± 7.99	.11	89.10 ± 7.72	.10
MAP mm Hg final	98.40 ± 11.08	104.80 ± 10.00	.38	109.50 ± 10.05	.05	109.00 ± 9.88	.07
ΔMAP%	21.70 ± 5.12	20.60 ± 4.11	.90	23.10 ± 4.18	.81	22.30 ± 3.80	.98
CPP mm Hg initial	78.68 ± 6.77	79.80 ± 8.92	.99	80.91 ± 9.16	.91	82.39 ± 8.41	.71
CPP mm Hg final	91.15 ± 6.79	97.23 ± 9.11	.34	100.53 ± 7.38	.08	101.15 ± 9.37	.06
ΔCPP mm Hg	16.09 ± 7.22	22.11 ± 4.71	.22	24.86 ± 8.55	.47	23.04 ± 6.88	.14
ICP mm Hg initial	8.93 ± 5.88	9.60 ± 4.77	.99	9.28 ± 5.00	1.00	9.70 ± 4.84	.98
ICP mm Hg final	9.55 ± 6.18	9.56 ± 4.85	1.00	8.84 ± 4.90	.99	9.88 ± 5.50	1.00
ΔCVR%	22.66 ± 14.26	15.02 ± 7.18	.41	22.26 ± 11.52	.99	19.09 ± 13.39	.86
sROR% (CPP)	150.89 ± 84.37	75.22 ± 27.75	.08	128.25 ± 58.35	.84	104.82 ± 36.92	.42
sROR% (MAP)	110.01 ± 77.97	80.45 ± 33.63	.55	91.78 ± 35.23	.82	89.79 ± 54.82	.77
PI	1.37 ± 0.39	1.41 ± 0.32	.99	1.46 ± 0.45	.92	1.43 ± 0.36	.98
V_{MCA} cm/s initial	67.50 ± 24.50	64.67 ± 21.38	.98	60.28 ± 18.57	.81	60.33 ± 19.40	.82
V_{MCA} cm/s final	66.63 ± 22.17	68.33 ± 22.72	1.00	61.00 ± 17.94	.90	62.67 ± 22.43	.96
$PtiO_2$ mm Hg initial	24.9 ± 14.8	22.7 ± 18.5	.99	22.5 ± 18.3	.99	22.9 ± 17.7	.99
$PtiO_2$ mm Hg final	24.9 ± 16	24.3 ± 18.9	1.0	23.7 ± 19.3	1.0	24.6 ± 18.6	1.0
NIRS % initial mean	71.5 ± 10.4	72 ± 11	1.0	69.7 ± 11.5	.97	69.5 ± 10.5	.96
NIRS % final mean	72.3 ± 9.7	72.6 ± 10.8	1.0	71.3 ± 11.2	.99	70.8 ± 10.7	.98

Note: The results during each dose of dexmedetomidine were compared to baseline. PI, sROR% and V_{MCA} are reported as an averaged value for both sides. The table also shows the brain tissue oxygenation, $PtiO_2$, and near infrared spectroscopy (NIRS) values during baseline and each dose of dexmedetomidine. The NIRS values are mean values of both sides. No significant difference was seen between the doses. MAP, mean arterial pressure; CPP, cerebral perfusion pressure; ICP, intracranial pressure; CVR, cerebrovascular resistance; sROR, static rate of autoregulation; PI, pulsatility index; V_{MCA}, velocity of the blood flow the middle cerebral artery; $PtiO_2$, brain tissue oxygenation; NIRS, near infrared spectroscopy.

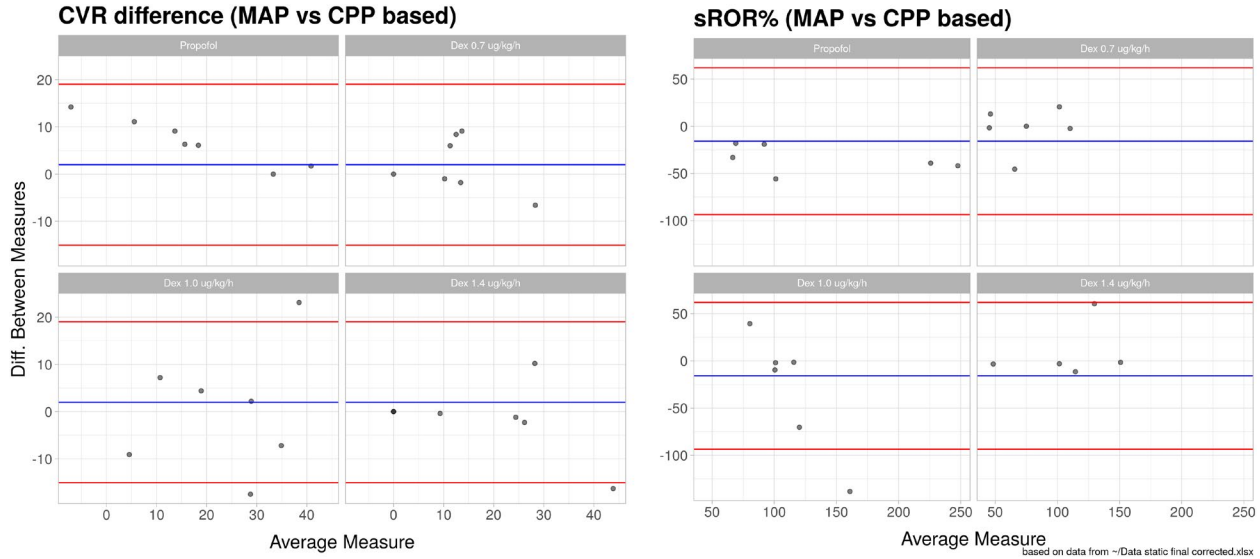

FIGURE 5 A Bland-Altman plot to compare the agreement of the sROR% measurements using MAP or CPP

dynamic strength of autoregulation) and static autoregulation when static rate of autoregulation is used.[27,31] However, various methods are probably not interchangeable[32,33] and there is no general consensus on how autoregulation should be monitored.[29]

Dynamic autoregulation has previously been shown to be impaired in healthy volunteers after administration of dexmedetomidine.[7] In this study, we found that the SA was significantly lower after the 1.0 μg/kg/h dose of dexmedetomidine compared to baseline, but not after the initial 0.7 μg/kg/h or the highest dose 1.4 μg/kg/h. It is possible that the effect of dexmedetomidine on dynamic autoregulation may be dose dependent in this population. Also, the ICP was not elevated in our patients and hence, they may have been less susceptible to any autoregulatory impairment with dexmedetomidine. Elevated ICP is known to correlate with impaired cerebral autoregulation.[34] In previous volunteer studies, dexmedetomidine administration was associated with decrease in MAP, cardiac output and CBF.[7,35] In contrast, we kept the blood pressure constant during dexmedetomidine infusion and THRT which may explain to some extent why there were no changes in most of the autoregulation indices. Dexmedetomidine induced reduction in CBF has been shown to be less in patients with traumatic brain injury if blood pressure is maintained at the pre-sedation level.[36] We used noradrenaline infusion in maintaining and increasing MAP and CPP levels.[37] Consequently, it is possible that autoregulatory impairment was not detected. It is possible that autoregulation was intact within the blood pressure range studied but may have been impaired outside of that range.

During the first days after aSAH, many patients have low CBF regardless of vasospasm or DCI.[38] The global CBF in patients with Fisher grade 4 aSAH is lower than in patients with Fisher grade 3, the impact of Fisher grade on CBF being more profound than the Hunt & Hess grades.[38] Since 8 of our 10 patients had Fisher grade 4 aSAH, it is unlikely that the heterogeneity of Hunt & Hess grades had an effect on our findings.

Our study has important limitations. Firstly, the sample size is small and larger studies are needed to confirm our preliminary findings. Secondly, the baseline sedation was not the same in all the patients. While most patients had propofol-infusion, two had midazolam-infusion, one had both and one had no sedation. The patients were continuously sedated for a few days before administration of dexmedetomidine which can confound autoregulation status. Ogawa et al found that midazolam seems to improve whereas propofol seems to have no effect on dynamic cerebral autoregulation in healthy volunteers.[39] In patients with traumatic brain injury, large, doses of propofol (more than 4 mg/kg/h) have been shown to impair static autoregulation.[30] We discontinued propofol 2 hours before the first and almost 6.5 hours before the last autoregulation assessments. After > 12 hours of infusion of propofol, it takes 3.5 hours to reduce the plasma concentration to 20%.[40] Therefore, the likelihood of residual propofol affecting cerebral autoregulation is small. Midazolam, on the other hand, may have had an effect on the dynamic autoregulation in our patients but only three patients were administered midazolam. Next, TCD only provides an estimate of CBF and it is assumed that the diameter of basal cerebral arteries varies only minimally with changes in MAP.[41,42] This presumption has been recently challenged and TCD observations should be carefully interpreted for CBF.[43] Fourth, we performed the study during the first days after aSAH, before the DCI usually appears and it is possible that autoregulatory status may change over time.

In conclusion, our preliminary findings indicate that in patients with aSAH, there was no difference in static cerebral autoregulation between dexmedetomidine and propofol and/or midazolam. The dynamic SA values, however, were significantly lower after 1.0 μg/kg/h dose of dexmedetomidine when compared to propofol and/or midazolam. This finding suggests that a sudden decrease in arterial blood pressure in aSAH patients during dexmedetomidine sedation

may not be desirable. These findings warrant further studies with larger sample size.

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CONFLICTS OF INTEREST

Dr Takala is a minor stock owner of Orion Corporation and Oriola. Dr Takala has received speaker's fee from Orion Corporation, Abbott, Baxter, Fresenius Kabi and UCB and travel grants from Steripolar and Pfizer. Dr Posti has received speaker's fees from Orion Corporation and Finnish Medical Association and a travel grant from Stryker Corporation. Dr Grönlund has received speaker's fees from Orion Corporation. Dr Saari has received speaker's fees from Orion Corporation. Dr Frantzén has received speaker's fees from Orion Corporation and Teva Pharmaceutical Industries and a travel grant from Abbot.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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