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Volatile sedation with sevoflurane in intensive care patients with acute stroke or subarachnoid haemorrhage using AnaConDa®: an observational study†

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Abstract

Background: The anaesthetic conserving device, AnaConDa®, allows use of inhaled anaesthetics for sedation in the intensive care unit. We prospectively measured cerebral and cardiopulmonary parameters in patients with acute stroke or subarachnoid haemorrhage during a switch from i.v. to inhalative sedation.

Methods: 25 patients were switched from i.v. to an indefinite period of inhaled sedation with sevoflurane. Mean arterial (MAP), intracranial (ICP), and cerebral perfusion pressure (CPP), middle cerebral artery mean flow velocity (MFV) and fractional tissue oxygen extraction (FTOE), systemic cardiopulmonary parameters, and administered drugs were assessed before and after the change (−6 to +12 h).

Results: In 8 patients, critically reduced MAP or ICP crisis led to premature termination of sevoflurane sedation. In the other 17 patients, after the first hour, mean ICP increased [2.4 (4.5) mm Hg; *P*=0.046], MAP decreased [7.8 (14.1) mm Hg; *P*=0.036] and thus CPP decreased also [−10.2 (15.1) mm Hg; *P*=0.014]. MFV and FTOE did not change. Over a 12 hour post switch observational period, Pa_{CO_2} increased slightly [0.3 (0.8) kPa; *P*=0.104], ICP did not change [0.2 (3.9) mm Hg; *P*=0.865], but MAP [−6 (6.9) mm Hg; *P*=0.002] and thus CPP decreased [−6 (8.5) mm Hg; *P*=0.010].

Conclusion: Sevoflurane led to sufficient sedation, but decreased MAP and CPP in a selected cerebrovascular neurocritical care population. In about a third of these patients, severe adverse reactions, including intolerable ICP increases, were observed.

Key words: critical care; inhalation anesthetics; sevoflurane; stroke

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Editor's key points

- The AnaConDa device facilitates the administration of inhalation agents for ICU sedation.
- Uncertainty exists about the safety of inhalation sedation in patients with neurological injuries.
- The Anaconda was used to administer sevoflurane sedation to stroke and subarachnoid haemorrhage victims.
- Many patients developed decreases in cerebral perfusion pressure and some raised intracranial pressure.

With the introduction of an anaesthetic conserving device (AnaConDa®) in 2005, the use of sevoflurane for ICU sedation has become practical and technically feasible.[1] Experimental animal research indicating that volatile anaesthetics may induce ischaemic preconditioning and have neuroprotective effects has sparked interest in the use of such agents for neurocritical care unit (NCCU) sedation.[2] However, reports on the danger of increasing intracranial pressure (ICP) as a result of cerebral vasodilation has discouraged their use for years.[2] With regard to sevoflurane, reports on its influence on cerebral haemodynamics are contradictory and focus on general anaesthesia for surgical procedures instead of sedation in a (neuro)intensive care environment. As a result, the safety and feasibility of sevoflurane for sedation in the NCCU is unclear.[3–10] With a more widespread administration of sevoflurane to ICU patients with primary or secondary brain injury, potential benefits as well as harms might go unnoticed if multimodality neuromonitoring is not utilized. To clarify the potential benefits and safety concerns regarding sevoflurane sedation, we prospectively analysed the switch from i.v. sedation to inhaled sevoflurane sedation administered via AnaConDa® in ventilated critical care stroke patients under multimodality monitoring. We assessed the short- and long-term effects on cerebral and systemic haemodynamics, oxygenation, and respiratory parameters.

Methods

Study setting and patient selection

Approval of the responsible Ethics Committee Heidelberg (S-188/2009) was obtained before starting this prospective, single-centre, observational study. Patients admitted to the Heidelberg University Hospital NCCU between March 2010 and December 2011 (thereafter, our in-house sedation protocol was changed) were screened. Inclusion criteria were: (I) acute cerebrovascular event (ischaemic stroke (IS), intracerebral haemorrhage (ICH), or subarachnoid haemorrhage (SAH)); (II) mechanical ventilation; (III) multimodality neuromonitoring as indicated by the attending physician (at least continuous ICP monitoring and Doppler capacity); and (IV) written informed consent of the patient's legal representative (for study participation and anonymous publication). Exclusion criteria were: (I) severely impaired pulmonary gas exchange (e.g., partial arterial oxygen pressure (Pa_{O_2}) <8 kPa (60 mm Hg) despite fractional inspiratory oxygen ($F_{I_{O_2}}$) > 0.6 and PEEP >10 cm H_2O); (II) refractory ICP crises (>25 mm Hg) lasting longer than 5 min and not responding to osmotherapy; (III) history or family history of malignant hyperthermia; and (IV) inclusion in any other trial influencing the sedation regime.

Ventilation and sedation

We used the pressure-controlled ventilation mode via SERVO-s® and SERVO–i® respirators (MAQUET, Rastatt, Germany) and ventilator settings were set to lung-protective target values (tidal volume <6 ml kg^{-1} body weight; avoidance of high inspiratory and peak pressures above 30 cm H_2O). Tidal volume was calculated according to the predicted body weight (PBW (kg)= $X + 0.91 \times$ (height (cm) − 152.4 cm); with X_{men}=50 and X_{women}= 45.5; www.ardsnet.org). Ventilator settings were adjusted according to blood gas analysis parameters (target Pa_{O_2} 9.3–13.3 kPa (70–100 mm Hg), Pa_{CO_2} 4.7–6 kPa (35–45 mm Hg), $Sa_{O_2} \geq 96\%$, pH 7.35–7.45). Patients were initially sedated with propofol or midazolam (in patients with propofol-induced hypotension) in combination with an opioid analgesic drug (remifentanil or sufentanil) according to our in-house standard. The Richmond Agitation Sedation Scale (RASS) was used to monitor the depth of sedation during the whole NCCU stay (target range −5 to −4 during the first days of the acute disease and in the study period). Sevoflurane was administered using AnaConDa® (technical details are described in[1 11 12]). Briefly, the AnaConDa® syringe was filled with sevoflurane, before connecting the device between the patient and respirator. It was filled with a 1.5 ml bolus, and additional 0.1 ml boli were administered until gas was registered at the monitor. Airway sevoflurane concentration and expiratory CO_2 were measured and minimum alveolar concentration (MAC) was calculated using a gas monitor (Scio Four Oxi plus, Dräger; Lübeck, Germany) connected to our standard monitoring system (Infinity Delta, Dräger; Lübeck, Germany). MAC values were automatically adjusted for age (1 MAC_{age}=1 $MAC \times 10^{bx}$, with b =− 0.00269[yr^{-1}] and x=age −40; Dräger®). After switching to sevoflurane, we aimed to reduce and eventually stop i.v. sedation as soon as the MAC reached 0.5.

Systemic monitoring

All vital signs and cardiorespiratory parameters were documented at least hourly during the transition period (−6 to +12 h). Heart rate (HR) was measured by using continuous ECG. Mean arterial pressure (MAP) was measured via a radial arterial line with the pressure sensor at the level of the heart. Partial arterial oxygen pressure (Pa_{O_2}), partial arterial carbon dioxide pressure (Pa_{CO_2}), pH, base excess (BE), and HCO_3^- were measured by blood gas analysis at least every other hour and arterial blood oxygen saturation (Sa_{O_2}) was calculated from the blood gas measurements using Siemens™ RAPIDLab/Point® (Siemens Healthcare GmbH, Eschborn, Germany). Central venous oxygen saturation (Scv_{O_2}) was measured in blood drawn from a central line inserted in the internal jugular (n=22) or subclavian vein (n=3). Urinary bladder temperature was monitored. Respiratory rate (RR), PEEP, peak inspiratory pressure, fractional inspiratory oxygen ($F_{I_{O_2}}$), and minute volume (MV) were directly assessed from the respirator. Pulmonary oxygenation was calculated as $Pa_{O_2}/F_{I_{O_2}}$.

Neuromonitoring

Patients were studied in the supine position with the head elevated by 20° during the sedation transition. A parenchymal probe (Neurovent-P®, Raumedic®, Münchberg, Germany) or external ventricular drain (EVD; Neurovent®, Raumedic®, Münchberg, Germany) provided continuous measurement of ICP. Zero reference level of the EVD was set to the ear in a vertical extension device for automatic adjustment of EVD drip chambers and ICP transducers. Cerebral perfusion pressure (CPP) was calculated as MAP-ICP.

As the MAP reference point was set to the level of the heart, the actual CPP level was estimated to be 5–10 mm Hg lower.[13 14] Regional cerebral oxygen saturation (rS_{O_2}) was measured by bifrontal near-infrared spectroscopy (NIRS; INVOS™ 5100, Covidien,

Mansfield, MA) and the cerebral arteriovenous oxygen saturation difference was calculated as $Sa_{O_2} - rS_{O_2}$. Fractional tissue oxygen extraction (FTOE) was calculated as $(Sa_{O_2} - rS_{O_2})/Sa_{O_2}$, as FTOE as the individual's oxygen extraction referencing to the individual patient's own arterial saturation has been found more robust and valid than the rS_{O_2} on its own at least in paediatric patients.[15] The systemic arteriovenous oxygenation difference was calculated as $Sa_{O_2} - Scv_{O_2}$. Middle cerebral artery mean flow velocity (MFV) was measured by transtemporal duplex/Doppler sonography (LOGICe; GE Healthcare, München, Germany) and calculated as 1/3 ($v_{systolic} + 2v_{diastolic}$). FTOE and MFV were separately calculated for the affected and nonaffected hemisphere. In patients whose lesions were bilateral or diffuse (such as in SAH), the side with more swelling and decompressive surgery was defined as 'affected' in two patients and the side of the aneurysm was defined as 'affected' in a third patient. Cerebrovascular resistance (CVR) was calculated as MAP/MFV for each hemisphere. FTOE and MFV, assessed bilaterally, and systemic oxygenation parameters were registered 1 h before and 1 h after the sedation switch, allowing systemic and ventilatory parameters to be kept mostly unchanged. ICP, MAP, and CPP were additionally measured and calculated at least hourly from 6 h before to 12 h after the sedation switch. All our in-house standard operating procedures for mechanical ventilation and weaning, normothermia, ICP and MAP/CPP management, and transfusion (target haemoglobin >8 g dl^{-1}) were continuously applied during the study. We predefined the following safety values to trigger corrective measures: ICP >25 mm Hg, MAP <80 mm Hg, CPP <60 mm Hg, $Sa_{O_2} < 90\%$, $Scv_{O_2} < 70\%$, and $rS_{O_2} < 50\%$ or 20% decrease from baseline.

Statistical analysis

Recorded and calculated parameters were described by mean (SD) or median (IQR); for categorical data we calculated absolute and relative frequencies (count and %). Shapiro-Wilk test was used to ascertain distribution of data. Measurements before and after the switch were compared by paired Student's *t*-test for normally distributed data and Wilcoxon's signed-rank test for not normally distributed. Unpaired *t*-test, Mann-Whitney *U*-test (for continuous variables) or the χ^2 test (for categorical data) were used to assess whether the distribution of baseline parameters differed between the patients who were successfully switched and those who were not. All *P*-values are descriptive and no adjustment for multiple comparisons was made; $P < 0.05$ is regarded significant. Explorative post-hoc analysis of subgroup differences was performed by repeated measures analysis of variance with time as the within-subject factor and diagnosis (or gender) as the between-subject factor. IBM™ SPSS® Version 22 and GraphPad Prism (6.0b) were used for data analysis.

Results

Patients

Of 907 patients admitted to our NCCU, 177 received multimodality neuromonitoring and 152 were ventilated >24 h. 127 patients had to be excluded because they were either participating in other interventional trials (majority) or met at least one other exclusion criterion, resulting in 25 patients finally being included in the study (Table 1).

Feasibility and safety

Initial sedatives were propofol in 16 patients, midazolam in 4 patients, and a combination of these in 5 patients. During transition to sevoflurane, 8 out of 25 patients (32%) displayed severe adverse reactions such as critical ICP elevations, forcing us to switch back to the initial i.v. sedative during the first 12 h after the switch. Sedation switch was done in successfully switched patients at day 3.8 (3.7), and in unsuccessfully switched at day 2.9 (2.5, *P*=0.545). The latter ones were excluded from our main analysis of long- and short-term effects, as AnaConDa® use was stopped for safety concerns, and details of these patients are described separately (see below). The remaining majority of patients (*n*=17; 68%) continued with volatile sedation for 4.18 (2.53) days.

Short-term analysis

Comparing cerebrovascular and systemic parameters 1 h before to 1 h after the switch, we observed an increase in ICP [+2.4 (4.5) mm Hg; Fig. 1, Table 2] , a decrease in MAP [−7.8 (14.1) mm Hg] and a decrease in CPP [−10.2 (15.1) mm Hg; Fig. 1(A)]. These changes occurred despite raising the dose of vasopressors. Propofol and midazolam doses were reduced, but could not be completely withdrawn early in two patients who still required parallel sedation with propofol (#2) or midazolam (#8) up to 5 h after the switch before stable sedation with sevoflurane was reached. We observed an increase in Pa_{CO_2} [0.5 (0.6) kPa], but CVR remained stable. An increase in central venous oxygen saturation but no change in arterial oxygen saturation (Sa_{O_2}) led to a reduction in the systemic arteriovenous oxygen difference. Neither the cerebral arteriovenous oxygen difference (Sa_{O2}-rS_{O2}) nor FTOE changed significantly.

Long-term analysis (−6 to +12 h)

While ICP remained stable, MAP decreased [−6 (6.9) mm Hg], thus reducing CPP [−6 (8.5) mm Hg; Fig. 1, Table 3] also. This decrease in blood pressure occurred despite attempts to counteract it by increasing noradrenaline. Fluid in- and output did not change relevantly during the transition period. Analgesia with remifentanil was kept constant in most patients, but was switched to equivalent doses of sufentanil in two patients before switch (−5, −4 h), and in two patients after switch (+4, +10 h) of sedation.

Pa_{CO_2} was stabilized to near baseline by increasing MV (mainly by increasing the respiratory rate and at times by slightly increasing peak and mean inspiratory pressures, if still necessary). Blood gas analysis additionally revealed metabolic acidosis (Fig. 1, Table 3). No renal impairment attributable to sevoflurane was observed comparing the baseline values (days −2 to −1) to those after switch (days 1–3) for creatinin (0.03 (−0.08; 0.193) mg dl^{-1}, *P*=0.35), GFR (−4.3 (−18.6; 13.3) ml min^{-1}, *P*=0.18) and blood urea nitrogen (−0.17 (−6.55; 11.9) mg dl^{-1}, *P*=0.59). Additionally, we found no significant influence of disease subgroups or gender on cerebral and systemic parameters.

Adverse reactions

In the 17 of 25 patients, cerebral and systemic parameters changed as described above, but remained inside tolerable thresholds. However, severe adverse reactions in eight other patients required early termination of sevoflurane administration. In one patient (#18, Table 1), systolic blood pressure (SBP) could not be maintained above 100 mm Hg and it repeatedly decreased below 80 mm Hg, despite steadily increased vasopressor support. Although a MAC of 1.5 was reached, the patient developed ventilator-patient dyssynchrony and required concomitant administration of propofol and rocuronium. Sevoflurane sedation was

Table 1 Baseline clinical patient characteristics (N=25). y, years; m, male; f, female; ICH, intracerebral haemorrhage; IS, ischaemic stroke; IVH, intraventricular haemorrhage; SAH, subarachnoid haemorrhage; ml, ICH volume [L^{-3}]; L, left; R, right; B, bilateral; AT, atypical (lobar); BG, basal ganglia (non-lobar); ds, decompressive surgery; he, haematoma evacuation; clip, aneurysm clipping; MCA, middle cerebral artery; ACA, anterior cerebral artery; GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health stroke scale[16]; ICP, intracranial pressure; E, external ventricular drain; P, parenchymal ICP probe; ICU, intensive care unit. *a* on day 3 complete MCA infarction on the left side with haemorrhagic transformation and immediate decompressive surgery; *b* predominant side of blood localization; *c* endoscopic; *d* Scores: ICH, The ICH Score[17]; G, Graeb score of IVH[18]; HH, Hunt and Hess scale of SAH[19]; F, Fisher scale of SAH[20]

	No.	Age (y)	Sex	Diagnosis	Features			GCS	NIHSS	modified Rankin scale score		Surgery	ICP probe	Sevoflurane in OR	ICU length of stay (days)	Volatile sedation duration (days)
					Lesion side	Territory/ Volume	Score[d]	on	admission	before ictus	at discharge					
Successful switch (N=17)	1.	67	f	ICH + IVH	L	BG; 57ml	ICH 4; G 6	3	33	1	5		E		19	6
	2.	80	f	ICH + IVH	R	BG; 20 ml	ICH 3; G 8	8	21	3	6		E		4	3
	3.	60	m	ICH + IVH	L	AT; 42 ml	ICH 4; G 7	3	30	1	5		E		12	10
	4.	77	m	ICH + IVH	L	BG; 10 ml	ICH 2; G 2	11	15	0	5		E		17	5
	5.	48	m	ICH + SAH	L	BG; 45 ml	ICH 3; F 2	3	37	1	5	ds	P		23	3
	6.	73	m	ICH	L	AT; 100 ml	ICH 2	7	27	0	4	he	P	x	13	1
	7.	46	m	IS	L	MCA, ACA		3	36	0	5	ds	P	x	12	2
	8.	48	f	IS	L	2/3 MCA		13	17	0	4	ds	P	x	18	6
	9.	62	m	IS	R	2/3 MCA		14	16	1	5		E		29	8
	10.	72	f	IS	L	cerebellar		7	14	1	5	ds	E	x	15	3
	11.	52	m	IS	R	MCA, ACA		13	18	0	5	ds	P		13	2
	12.	69	m	IS	R	MCA,ACA		11	15	0	6		P		6	1
	13.	75	m	IS	R	MCA		7	17	0	5	ds	P	x	13	4
	14.	68	f	IS	L	MCA		13	20	0	5	ds	P	x	13	4
	15.	61	m	IVH	R[b]		G 7	3	37	1	5		E		17	7
	16.	37	f	SAH[a]	B		HH 2, F4	14	1	0	6	clip, ds	P		14	2
	17.	61	m	SAH + ICH	B	BG; 45 ml	ICH 4; HH 4, F 4	3	37	0	5		E		26	4
Early termination (N=8)	18.	73	f	ICH	L	AT; 80 ml	ICH 4	12	30	2	5	he	P	x	8	11 h
	19.	47	m	ICH + IVH	L	BG; 2 ml	ICH 2; G 10	14	10	0	4		E		14	7 h
	20.	71	m	ICH + IVH	R	AT; 140 ml	ICH 1; G 6	9	21	3	6	he	P	x	5	3.5 h
	21.	65	f	ICH + IVH	R	BG; 78 ml	ICH 3; G 8	3	32	0	5	he	E	x	13	1 h
	22.	56	m	ICH	L	BG; 70 ml	ICH 4	11	20	0	5	he	P	x	28	<1 h
	23.	75	m	ICH	L	AT; 55 ml	ICH 3; G 8	3	31	1	6	he[c]	E	x	11	<1 h
	24.	43	f	IS	B	MCA, ACA		10	28	3	5	ds	P	x	15	6 h
	25.	75	m	IVH	L[b]		G 9	11	20	0	5		E		17	1 h

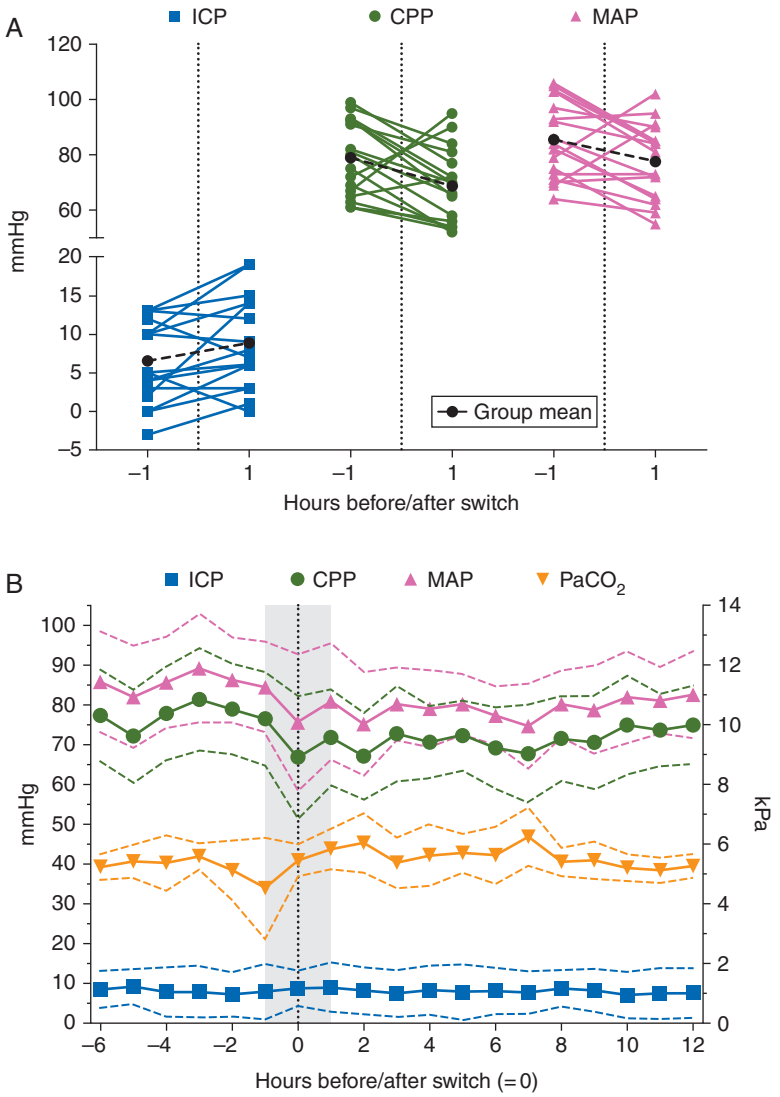

Fig 1 (A) Individual short-term changes in ICP, CPP, and MAP 1 h before and 1 h after switching to sevoflurane sedation. (B) Long-term dynamics of ICP, CPP, MAP and Pa_{CO_2} from 6 h before to 12 h after switch (hourly means and standard deviations (dashed-lines)).

stopped after 10.5 h and bp immediately rose and stabilized. In a second patient (#20), a rapidly increasing demand for vasopressors forced us to stop sevoflurane 3.5 h after initiation. Insufficient sedation alone occurred in a third patient (#19), who required additional bolus doses of midazolam. Because of recurrent ventilator patient dyssynchrony, we had to stop sevoflurane after 7 h. The most common adverse reaction, however, was a critical increase in ICP. In 3 of the 5 patients affected (#23–25), ICP reached >25 mm Hg, and in 2 patients (#21,22) we even observed levels >30 mm Hg. Of note, in 4 out of the 5 patients critical ICP elevation occurred within the very first hour of sevoflurane administration (Fig. 2). Two patients were subsequently switched to isoflurane, which normalized their ICP values and allowed stable sedation in both patients. Notably, patients who didn't tolerate the switch had a higher baseline ICP (12.5 *vs* 7.8 mm Hg, P=0.03). The proportion of patients suffering from ICH seemed to be higher in patients who developed adverse reactions than in those who did not (75 *vs* 35.3%), and, although not significant, ICH volumes were larger (70.8 *vs* 45.6 ml, P=0.244). No changes in analgesia were made within the sevoflurane sedation period, but in one patient remifentanil was switched to sufentanil simultaneously with withdrawal of sevoflurane, and in another patient after withdrawal of sevoflurane. There was no difference between the mean MAC values in patients successfully switched and the early termination group (+1 h until stop) (0.6 *vs* 0.58, P=0.872). In the patients suffering adverse events, we found significantly higher Pa_{CO_2} levels after switch (5.1 *vs* 6 kPa, P=0.013). However, when analyzing the latter in only those patients in whom ICP elevations or crisis were the relevant factor for early termination of sevoflurane sedation, no significant difference was found (5.1 *vs* 5.8 kPa, P=0.151). Adverse reactions could not be convincingly attributed to development of cerebral oedema, re-bleeding, technical failures with the AnaConDa®, or painful procedures.

Table 2 Short-term changes in systemic and cerebral monitoring parameters (n=17). ICP, intracranial pressure; MAP, mean arterial pressure; CPP, cerebral perfusion pressure; MFV, mean middle cerebral artery flow velocity; Sa_{O_2}, arterial blood oxygen saturation; Scv_{O_2}, central venous oxygen saturation; rS_{O_2}, regional cerebral tissue oxygen saturation; FTOE, fractional tissue oxygen extraction; Pa_{CO_2}, partial arterial pressure of carbon dioxide; CVR, cerebrovascular resistance; MAC, minimum alveolar concentration; et%, end-tidal concentration. Affected/non-affected refers to the hemisphere with/without the primary lesion. Data on MFV were not available in 8, on Sa_{O_2} in 3, on Scv_{O_2} in 6, on rS_{O_2} in 5, Pa_{CO_2} in 3 and FTOE in 8 patients (partially overlapping) for diverse technical reasons. [a]Patients receiving dobutamine: n=3 before, n=4 after s witch. Data are mean (SD) or median (IQR). 95% CI, confidence interval of the mean

	Hemisphere	Before Switch (−1 h)	After Switch (+1 h)	Difference	95% CI	P-value
ICP (mm Hg)		6.53 (5.19)	8.88 (5.83)	2.35 (4.49)	0.05–4.66	0.046
MAP (mm Hg)		85.41 (14.04)	77.59 (13.61)	−7.82 (14.09)	−15.07–−0.58	0.036
CPP (mm Hg)		78.88 (13.35)	68.71 (13.49)	−10.18 (15.14)	−17.96–−2.39	0.014
MFV ($cm\ s^{-1}$)	affected	65.33 (30.83)	73 (21.64)	7.67 (30.55)	−15.81–31.15	0.473
	nonaffected	66.80 (44.61)	73.11 (34.22)	2.56 (36.8)	−25.73–30.84	0.840
Sa_{O_2} (%)		80.82 (38.58)	97.93 (1.33)	−0.21 (0.8)	−0.68–0.25	0.336
Scv_{O_2} (%)		78.09 (3.75)	82.08 (4.42)	3.36 (4.55)	0.31–6.42	0.034
rS_{O_2} ($cm\ s^{-1}$)	affected	74.08 (6.13)	71.92 (6.64)	−1.33 (4.08)	−3.92–1.26	0.281
	nonaffected	68.92 (6.64)	69.5 (5.11)	1.17 (5.62)	−2.41–4.74	0.487
$Sa_{O_2} - rS_{O_2}$ (%)	affected	24.08 (6.83)	26.17 (6.77)	1 (4.07)	−1.58–3.58	0.413
	nonaffected	29.23 (7.40)	28.58 (5.85)	−1.5 (5.7)	−5.12–2.12	0.381
$Sa_{O_2} - Scv_{O_2}$ (%)		20.18 (4.14)	15.67 (5.00)	−3.73 (4.32)	−6.63–−0.83	0.017
FTOE	affected	0.24 (0.07)	0.27 (0.07)	0.01 (0.04)	−0.01–0.04	0.369
	nonaffected	0.30 (0.07)	0.29 (0.06)	−0.01 (0.06)	−0.05–0.02	0.408
Pa_{CO_2} (kPa)		5.3 (0.6)	5.8 (0.7)	0.5 (0.6)	0.2–0.9	0.003
CVR (mm Hg $cm^{-1}\ s^{-1}$)	affected	1.49 (0.57)	1.24 (0.57)	−0.25 (0.6)	−0.71–0.21	0.248
	nonaffected	1.73 (0.99)	1.31 (0.76)	−0.38 (0.77)	−0.97–0.22	0.182
Propofol ($mg\ kg^{-1}\ h^{-1}$)		2.15 (0.63; 3.10)	0.83 (0; 1.83)	−0.5 (−2; 0)	–	0.004
Midazolam ($mg\ kg^{-1}\ h^{-1}$)		0 (0; 0.2)	0 (0; 0.1)	0 (0; 0)	–	0.250
Remifentanil ($\mu g\ kg^{-1}\ min^{-1}$)		0.06 (0; 0.12)	0.04 (0; 0.1)	0 (−0.01; 0)	–	0.125
Sufentanil ($\mu g\ kg^{-1}\ h^{-1}$)		0 (0; 0.99)	0 (0; 0.44)	0 (−0.43; 0)	–	0.063
Noradrenaline ($\mu g\ kg^{-1}\ min^{-1}$)		0.04 (0; 0.09)	0.04 (0.02; 0.1)	0.01 (0; 0.02)	–	0.042
Dobutamine[a] ($\mu g\ kg^{-1}\ min^{-1}$)		0 (0; 0)	0 (0; 0.59)	0 (0; 0.29)	–	0.125
Sevoflurane (MAC)		–	0.48 (0.18)			
Sevoflurane (et%)		–	0.89 (0.42)			

Discussion

In this prospective study of sevoflurane sedation in 25 critical care patients with acute stroke or subarachnoid haemorrhage, sufficient sedation levels without clinically relevant ICP increase were achieved in 68% of the patients. However, serious adverse events observed in the remaining 32% raise considerable safety concerns.

In view of the heterogeneous literature regarding the amount of sevoflurane's cerebrovasodilatory effect and consequent ICP elevation, our own previous overall positive experience with the supposedly more vasodilatory isoflurane, and the ability to use multimodality monitoring, we have considered it justified to study a preselected population without prior refractory ICP crisis.[3 4–6 9 10 21] Indeed, in the 17 patients successfully switched to sevoflurane, ICP increased only slightly in the short term and remained stable in the long term. However, MAP and thus CPP decreased. Our findings are in line with other studies, finding that intraoperative sevoflurane anaesthesia decreased MAP[8 9] while ICP remained stable in some studies[5 22] and increased in others.[6 9 23] Our study adds the novel insight that significant and relevant MAP/CPP reductions and at least transient ICP elevations, possibly linked to increases in Pa_{CO_2}, can already occur in the majority of patients at lower sedative doses of MAC (0.6 is typically sufficient in the ICU setting).

We did not observe a consistent short-term change in MFV, supporting previous studies in which MFV was also not found to be influenced by sevoflurane.[24 25] In addition, we found that sevoflurane did not reduce FTOE (i.e., did not improve cerebral oxygenation) unlike our findings for isoflurane in a previous study.[21] One possible explanation for this discrepancy is that the dose of sevoflurane was not high enough to affect rS_{O_2}, as a recent experimental trial in 44 patients undergoing abdominal hysterectomy found rS_{O_2} to be higher only at considerably higher doses of sevoflurane (max. MAC 1.8).[26]

Pa_{CO_2} increased under use of AnaConDa®, confirming experimental studies finding an increased CO_2 via AnaConDa®'s enlarged dead space and CO_2-conserving capacity.[27–30] Efforts to keep Pa_{CO_2} within the target levels required RR and MV to be increased significantly and, if still necessary, slightly higher peak and mean inspiratory pressures. In NCCU patients at risk for increased ICP, this effect of inhaled sedation underscores the necessity for tight control of Pa_{CO_2} as increases in Pa_{CO_2} may contribute to the short-term mean increase via hypercapnic vasodilatory effects.

Notably, one third of the patients experienced severe adverse reactions: ICP increased rapidly and MAP decreased in five patients, forcing us to stop sevoflurane sedation (which reversed the changes). These findings differed from our previous experience with isoflurane.[21] We consider several explanations for the observed differences: (a) a high percentage of patients may have had a low baseline cerebral compliance (for instance, patients not tolerating the switch to sevoflurane had larger volumes of ICH (albeit statistically non-significant) and tended to require pre-switch osmotherapy more often (Table 4)); (b) higher baseline ICP values in patients demonstrating adverse reactions

Table 3 Long-term parameter changes after switching to sevoflurane sedation (n=17). ICP, intracranial pressure; CPP, cerebral perfusion pressure; HR, heart rate; MAP, mean arterial pressure; RR, respiratory rate; MV, minute volume; Pa_{O_2}, partial pressure of arterial oxygen; $F_{I_{O_2}}$, fraction of inspired oxygen; Pa_{CO_2}, partial pressure of arterial carbon dioxide; PEEP, positive end-expiratory pressure; Ppeak, peak inspiratory pressure; Pmean, mean inspiratory pressure; BE, base excess; HCO_3^-, bicarbonate; MAC, minimum alveolar concentration. [a]i.v. sedation was fully discontinued after a max. of 2 h (2 pts., 5 h). Data are mean (SD) or median (IQR). 95% CI, confidence interval of the mean

	Before Switch (−6 to −1 h)	After Switch (1–12 h)	Difference	95% CI	P-value
Cerebral					
ICP (mm Hg)	7.80 (5.12)	7.96 (4.93)	0.16 (3.85)	−1.82–2.14	0.865
CPP (mm Hg)	77.46 (7.67)	71.45 (6.9)	−6.01 (8.51)	−10.38 to −1.64	0.010
Cardiovascular and systemic					
HR (min^{-1})	64.71 (12.76)	69.15 (13.53)	4.44 (13.2)	−2.35–11.22	0.185
MAP (mm Hg)	85.37 (7.96)	79.38 (6.4)	−5.99 (6.87)	−9.52 to −2.45	0.002
Fluid input (ml h^{-1})	225.1 (78.3)	200.4 (50.66)	−24.68 (76.89)	−64.21–14.86	0.204
Fluid output (ml h^{-1})	175.0 (87.89)	171.4 (64.83)	−3.60 (102.90)	−56.52–49.32	0.887
Temperature (°C)	36.39 (0.76)	36.28 (0.98)	−0.11 (0.86)	−0.55–0.34	0.621
Respiratory					
RR (min^{-1})	12.68 (1.79)	14.85 (2.02)	2.18 (1.83)	1.24–3.12	<0.001
MV (l min^{-1})	6.97 (1.02)	8.36 (1.31)	1.38 (0.96)	0.89–1.88	<0.001
$Pa_{O_2}/F_{I_{O_2}}$	313.6 (80.71)	298.5 (86.18)	−15.15 (64.91)	−48.52–18.22	0.350
$F_{I_{O_2}}$	0.37 (0.75)	0.38 (0.7)	0.13 (0.73)	−0.025–0.05	0.479
Pa_{CO_2} (kPa)	5.2 (0.5)	5.6 (0.5)	0.3 (0.8)	−0.1–0.8	0.104
PEEP (cm H_2O)	5 (5; 7)	6 (5; 7.33)	0 (0; 0.13)	–	0.138
Ppeak (cm H_2O)	19.89 (3.49)	21.89 (3.6)	2.01 (1.72)	1.12–2.89	<0.001
Pmean (cm H_2O)	10.64 (2.11)	11.76 (2.03)	1.12 (1.13)	0.54–1.7	0.001
Acid–base homeostasis					
BE	−0.09 (3.24)	−1.58 (3.13)	−1.49 (1.53)	−2.27 to −0.7	0.001
HCO_3^-	24.66 (2.9)	23.54 (2.6)	−1.11 (1.33)	−1.8 to −0.43	0.003
pH	7.41 (0.54)	7.37 (0.05)	−0.04 (0.05)	−0.06 to −0.00	0.006
Drugs					
Sevoflurane (MAC)	–	0.6 (0.2)	0.6 (0.2)	–	
Propofol[a] (mg kg^{-1} h^{-1})	2.15 (1.58; 3.14)	0.1 (0; 0.16)	−1.85 (−3.03; −1.22)	–	<0.001
Midazolam[a] (mg kg^{-1} h^{-1})	0 (0; 0.16)	0 (0; 0.01)	0 (−0.16; 0)	–	0.016
Remifentanil (µg kg^{-1} min^{-1})	0.07 (0; 0.12)	0.01 (0; 0.09)	−0.03 (0.05; 0)	–	0.002
Sufentanil (µg kg^{-1} h^{-1})	0 (0; 0.68)	0.28 (0; 0.44)	−0 (−0.35; 0.04)	–	0.232
Noradrenaline (µg kg^{-1} min^{-1})	0.04 (0; 0.09)	0.07 (0.04; 0.13)	0.03 (0.01; 0.06)	–	0.001

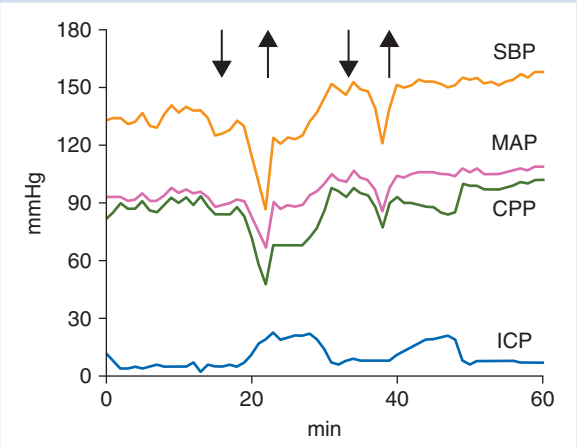

Fig 2 Rapid adverse haemodynamic reactions in a patient switched to sevoflurane sedation (arrow head down), which resolve after withdrawal (arrow head up). Stereotype reaction was observed after a second attempt to switch on sevoflurane. During switching attempts, parallel sedation was not modified (midazolam 0.17 mg kg^{-1} h^{-1}; sufentanil 1.1 µg kg^{-1} h^{-1}; noradrenaline 8.2 µg kg^{-1} min^{-1}). External ventricular drain was left open.

decreased the safety margin, although these baseline ICP values were still within acceptable ranges; (c) as cerebral autoregulation is better preserved under sevoflurane than under isoflurane,[3 31 32] vasodilation responding to the decrease in MAP and a more intensive reaction to raised Pa_{CO_2} might have caused ICP crises in patients with low cerebral compliance; and (d) although the hourly scored sedation depth was maintained at RASS −4 to −5 long-term, the sedation switch might have caused a transient stress response. We cannot rule out sympathetic activation which might have caused changes in cerebral metabolism and haemodynamics, but have not found conclusive evidence for it, as changes in minute volume were mainly the result of manual adjustments of ventilation parameters in order to achieve isocapnia, and heart rate did not change. As in the early termination group all parameters resolved to normal after sevoflurane was stopped and changed to a different sedative, we consider it unlikely that changes in the patients' condition itself could explain the observed adverse effects for the major part. Such drug-independent causes of the observed effects could theoretically have been for example increases in cerebral oedema, rebleeding, or seizures but no convincing hints at these conditions were present during the observational period in our population. We could not further elucidate the putative mechanisms underlying these adverse events, as we stopped administering sevoflurane for safety

Table 4 Comparison of baseline parameters. Data are presented as mean(SD) or numbers (%). NIHSS, National Institutes of Health stroke scale; GCS, Glasgow coma scale; ICH, intracerebral haemorrhage; IVH, intraventricular haemorrhage; IS, ischaemic stroke; SAH, subarachnoid haemorrhage; ICP, intracranial pressure; CPP, cerebral perfusion pressure; HR, heart rate; MAP, mean arterial pressure; RR, respiratory rate; MV, minute volume; Pa_{O_2}, partial pressure of arterial oxygen; $F_{I_{O_2}}$, fraction of inspired oxygen; Pa_{CO_2}, partial pressure of arterial carbon dioxide; PEEP, positive end-expiratory pressure; Ppeak, peak inspiratory pressure; Pmean, mean inspiratory pressure; BE, base excess; HCO_3^-, bicarbonate. [a]decompressive surgery: here subsuming craniectomy and haematoma evacuation. Data are mean (SD), median (IQR), or number (%)

	Successful switch (*N*=17)	Early termination (*N*=8)	*P*-value
Patient characteristics and clinical characteristics			
Age (years) (range)	62.1 (37–80)	63.1 (43–75)	0.853
Women	11 (64.7%)	5 (62.5%)	1.000
pre-stroke modified Rankin	0 (0; 3)	0.5 (0; 2.75)	0.381
NIHSS at admission	20 (15.50; 31.50)	29 (20.25; 31.75)	0.280
GCS at admission	8 (3; 13)	9.5 (3; 11.75)	0.828
Pts. with diagnosis			0.185
ICH	6 (35.3%)	6 (75.0%)	
IVH	1 (5.9%)	1 (12.5%)	
IS	8 (47.1%)	1 (12.5%)	
SAH	2 (11.8%)	0 (0%)	
Volume of ICH (ml)	45.6 (28.9)	70.8 (44.5)	0.244
ICH score	3.0 (2; 4)	3 (2; 4)	0.700
Graeb score	7 (4; 7.5)	8 (7; 9.5)	0.119
Decompressive surgery before switch[a] (*n* (%))	9 (52.9%)	6 (75.0%)	0.402
Osmotherapy before switch	6 (35.3%)	6 (75.0%)	0.097
Cerebral			
ICP (mm Hg)	7.8 (5.12)	12.5 (3.77)	0.030
CPP (mm Hg)	77.46 (7.67)	74.09 (10.69)	0.376
Cardiovascular and systemic			
HR (min^{-1})	64.71 (12.77)	66.87 (9.95)	0.678
MAP (mm Hg)	85.37 (7.96)	86.73 (10.22)	0.718
Fluid input (ml h^{-1})	225.1(78.3)	215.5 (113.5)	0.814
Fluid output (ml h^{-1})	175.1 (87.9)	169.2 (75.1)	0.879
Temperature (°C)	36.39 (0.76)	36.67 (0.58)	0.367
Respiratory			
RR (min^{-1})	12.68 (1.79)	12.68 (1.85)	0.999
MV (l min^{-1})	6.97 (1.02)	6.66 (1.19)	0.505
$Pa_{O_2}/F_{I_{O_2}}$	313.61 (80.71)	344.80 (103.20)	0.418
$F_{I_{O_2}}$	0.37 (0.75)	0.37 (0.74)	0.839
Pa_{CO_2} (kPa)	5.2 (0.5)	5.1 (0.3)	0.620
PEEP (cm H_2O)	5 (5; 7)	5 (5; 6)	0.358
Ppeak (cm H_2O)	19.89 (3.49)	19.30 (3.25)	0.693
Pmean (cm H_2O)	10.64 (2.11)	10.59 (2.76)	0.962
Acid–base homeostasis			
BE	−0.9 (3.24)	0.67 (2.47)	0.564
HCO_3^-	24.66 (2.9)	25.22 (2.30)	0.636
pH	7.41 (0.54)	7.43 (0.05)	0.264
Drugs			
Propofol (mg kg^{-1} h^{-1})	2.15 (1.58; 3.14)	3.09 (0.36; 3.76)	0.576
Midazolam (mg kg^{-1} h^{-1})	0 (0; 0.16)	0 (0; 0.13)	0.621
Remifentanil (µg kg^{-1} min^{-1})	0.07 (0; 0.12)	0 (0; 0.09)	0.315
Sufentanil (µg kg^{-1} h^{-1})	0 (0; 0.68)	0.70 (0; 1.05)	0.242
Noradrenaline (µg kg^{-1} min^{-1})	0.04 (0; 0.09)	0.09 (0.02; 0.17)	0.286

reasons. These findings were particularly worrying in retrospect, as 75% of the patients in the 'early termination' group had received standard sevoflurane anaesthesia during neurosurgery in the acute phase of their disease before this study (Table 1). However, during neurosurgery no ICP/CPP monitoring was in place, thus impeding conclusions about cerebral pressure dynamics at that time.

As a consequence for our daily in-house sedation practice, the high incidence of ICP crises and other adverse reactions, together with higher cost and substance consumption, prompted us to abandon sevoflurane sedation in our NCCU. We continue to use isoflurane with the AnaConDa® in selected patients under multimodality neuromonitoring (i.e. at least continuous monitoring of ICP and tight control of cardiopulmonary parameters).

Our study has several limitations. It was conducted as a single-centre, open-label observational study and treatment allocation was not randomized. Thus, no confirmatory analysis was planned and the reported *P*-values should be interpreted as

exploratory results only. Parameter assessment in a complex NCCU setting is prone to interfering factors. For instance, keeping Pa_{CO_2} absolutely constant would be desirable to detect independent vasodilating effects of a sedative drug. We could not fully normalize Pa_{CO_2} as lung-protective ventilation was one safety criterium and hence the increases in Pa_{CO_2} might have contributed to (transient) ICP elevations. Despite increases in vasopressor support, MAP did not reach baseline values after switch, which possibly confounds interpretation on effects on the local cerebral circulation and metabolism. This observation, however, indicates the problem of systemic hypotension connected to this form of sedation and the need of even more rigorous counterbalancing measures. Also, individual neuromonitoring devices may have their limitations. The NIRS has raised controversy because of its local, only trend-indicating and extracranially-susceptible characteristics, as well as possible influencing factors such as cerebral oedema, intracranial haematoma or blood staining of cerebrospinal fluid.[33 34] Scv_{O_2} has been used to estimate systemic venous oxygenation, but correlation with mixed venous oxygen saturation is still matter of debate.[35] We did not use bispectral index monitoring (BIS), which may have provided a more objective way to monitor sedation depth. Instead, the clinical RASS score, which correlates well with the BIS in NCCU patients, was used.[36]

This is so far the largest prospective study in neurocritical care addressing feasibility and safety of sevoflurane administered via the AnaConDa®. In conclusion, in a population of patients at high risk of intracranial hypertension, sevoflurane sedation was associated with major adverse events in one third of patients. In almost all of the patients, MAP had to be stabilized actively to maintain CPP. Based on these observations we do not feel that the alleged neuroprotective potential of sevoflurane outweighs the risk of adverse events and sevoflurane sedation should probably not be used in this specific patient population. If it is used, multimodality neuromonitoring is mandatory.

Authors' contributions

J.P.: participated in study conduction, collected and analysed data and wrote the manuscript. J.R.: collected and interpreted data. T. S., W.H.: participated in study initiation and revised the manuscript for important intellectual content. L.U., T.B.: provided important statistical advice. J.B.: conceived the study, developed the study design, enrolled patients, collected and analysed data, and reviewed the manuscript. All authors read and approved the final manuscript for publication.

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Declaration of interest

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