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Volatile isoflurane sedation in cerebrovascular intensive care patients using AnaConDa®: effects on cerebral oxygenation, circulation, and pressure

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Abstract *Purpose:* The anesthetic-conserving device AnaConDa®, a miniature vaporizer, allows volatile sedation in the intensive care unit (ICU). We investigated the effects of isoflurane sedation on cerebral and systemic physiology parameters in neuromonitored ICU stroke patients. *Methods:* Included in the study were 19 consecutive ventilated patients with intracerebral hemorrhage (12), subarachnoid hemorrhage (4), and ischemic stroke (3) who were switched from intravenous propofol or midazolam to inhalative isoflurane sedation for an average of 3.5 days. During the sedation transition, the following parameters were assessed: mean arterial pressure (MAP), intracranial pressure (ICP), cerebral perfusion pressure (CPP), middle cerebral artery mean flow velocity (MFV) and cerebral fractional tissue oxygen extraction (FTOE), as well as systemic cardiopulmonary parameters and administered drugs. *Results:* After the first hour, mean ICP showed an increase of 2.1 mmHg that was not clinically relevant. Likewise, MFV did not change. MAP and CPP, however, decreased by 6.5 and 6.3 mmHg, respectively. FTOE was reduced slightly from 0.24 to 0.21 ($p = 0.03$). Over an observation period of 12 h, ICP remained stable, while MAP and thus CPP showed distinct decreases (CPP: −10 mmHg at 6 h, $p < 0.001$; −7.5 mmHg at 12 h, $p = 0.005$, when compared to preswitch levels) despite a 1.5-fold increase in vasopressor administration. *Conclusions:* We suggest that that it is possible to reach sufficient sedation levels in cerebrovascular ICU patients by applying volatile isoflurane long-term without a relevant increase in ICP, if baseline ICP values are low or only moderately elevated. However, caution should be exercised in view of isoflurane's decreasing effect on MAP and CPP. Multimodal neuromonitoring is strongly recommended when applying this off-label sedation method.

Keywords Volatile anesthetics · Isoflurane · AnaConDa® · Stroke · Sedation · Analgesia

Introduction

The aims of sedation and analgesia in the intensive care unit (ICU) patient are to achieve freedom from pain, anxiety, agitation, and tolerance of mechanical ventilation [1, 2]. In neurocritical care, additional aims are to prevent seizures, to keep intracranial pressure (ICP) low and to stabilize impaired cerebrovascular autoregulation. Common intravenous sedatives, such as midazolam and propofol, in conjunction with opioids [3], are effective but tend to accumulate and/or have specific side effects. The volatile anesthetic isoflurane, established for general anesthesia in surgery, has recently become applicable outside the operating room (OR) following the introduction of a miniature vaporizer, the AnaConDa® (anesthetic conserving device; SEDANA Medical, Uppsala, Sweden), that can be connected to any ICU respirator [4]. Studies of the AnaConDa® system in mixed ICU populations have suggested advantages [5, 6], but reports in brain-injured patients are lacking. Although still off-label, inhalative ICU sedation is currently spreading all over Europe and has been recommended as an alternative in a recent German consensus guideline [2]. Previous studies on isoflurane have suggested its neuroprotective potential in cerebrovascular disease [7]. More recent reports, however, have raised concerns about neurotoxicity [8, 9]. Furthermore, isoflurane's reported potential to raise ICP via direct cerebral vasodilation [10–16] has discouraged its use in brain-injured patients who are prone to ICP increases. However, data only exist on the short-term OR but not the more long-term neurological ICU (NICU) setting.

In the light of these uncertainties but intrigued by isoflurane's potential as an alternative sedative and neuroprotectant, we prospectively investigated isoflurane's effects on cerebral and systemic hemodynamic parameters in neuromonitored ventilated stroke patients.

Methods

Patient inclusion and sedation management

Approval by our local ethics committee was obtained. All patients or their legal representatives provided written informed consent. Patients admitted to our university hospital NICU between October 2009 and April 2011 were screened for inclusion. Patients were included if they (a) had an acute cerebrovascular event, i.e. ischemic stroke (IS), intracerebral hemorrhage (ICH) or subarachnoid hemorrhage (SAH), (b) had to be ventilated, and (c) were equipped with multimodal neuromonitoring. Patients were excluded if (a) pulmonary gas exchange was severely impaired (as in oxygenation insufficiency, e.g. partial arterial oxygen pressure (PaO_2) <60 mmHg despite fractional inspiratory oxygen (FiO_2) >0.6 and positive end-expiratory pressure (PEEP) >10 mmHg), (b) they had refractory ICP crises (ICP >25 mmHg longer than 5 min, not responding to osmotherapy), (c) they had a family history of malignant hyperthermia, or (d) they were included in any other trial influencing the sedation regimen. Patients were ventilated in pressure-controlled mode and in a lung-protective fashion (tidal volume <6 ml/kg body weight, avoiding high inspiratory and peak pressures) by Servo respirators (MAQUET, Rastatt, Germany). According to our in-house ICU sedation standard operating procedure, patients were initially put on propofol or on midazolam if propofol induced hypotension. If analgosedation was expected to be necessary for <5 days, intravenous sedation was switched to volatile isoflurane sedation. Technical details of the AnaConDa® device are presented elsewhere [4, 6]. Isoflurane was coadministered until the gas monitor (Scio Four, Dräger; Lübeck, Germany) showed a minimal alveolar concentration (MAC) of 0.5, then the intravenous sedative was stopped. Thereafter, the isoflurane perfusion rate was adjusted to maintain the previous Richmond Agitation Sedation Scale (RASS [17]) score (target range −5 to −4), assessed from 6 h before to 6 h after sedation switch, and according to clinical and ventilation parameters. Patients were kept in the supine position with elevation of the head of the bed at 20° throughout the transition.

Systemic monitoring

Mean arterial pressure (MAP) and heart rate were measured via a radial arterial line with the pressure sensor at the level of the heart. Arterial blood oxygen saturation (SaO_2), PaO_2 and partial arterial carbon dioxide pressure ($PaCO_2$), pH, base excess and bicarbonate were measured via the same radial arterial line by regular blood gas analysis. Central venous oxygen saturation ($ScvO_2$) was measured via a jugular or subclavian central line. Respiratory rate, PEEP, peak inspiratory pressure, mean inspiratory pressure, fractional inspiratory oxygen (FiO_2), and minute volume were directly assessed from the respirator. Pulmonary oxygenation was calculated as PaO_2/FiO_2. Vital signs, fluid-in and fluid-out, bladder temperature and drug rates were documented at least hourly during the transition period (−6 to +12 h). Safety laboratory parameters including liver enzymes and renal parameters were documented at least every other day.

Neuromonitoring

Intracranial pressure was measured via a parenchymal probe (Raumedic; Münchberg, Germany) or an external ventricular drain (EVD, zero reference level at the ear in a

vertical extension device for automatic adjustment of EVD drip chambers or ICP transducers), and cerebral perfusion pressure (CPP) was calculated as MAP − ICP. Regional cerebral oxygen saturation (rSO_2) was measured by bifrontal near-infrared spectroscopy (NIRS) using an INVOS 5100 system (Covidien, Mansfield, MA) [18, 19]. Differences between systemic and cerebral arteriovenous oxygen saturation were calculated as SaO_2-$ScvO_2$ and SaO_2-rSO_2, respectively; and fractional tissue oxygen extraction (FTOE, [20] = cerebral oxygen extraction) was calculated as $(SaO_2 - rSO_2)/SaO_2$. As a surrogate indicator of cerebral blood flow [21], the middle cerebral artery mean flow velocity (MFV) was measured by transtemporal duplex/Doppler sonography (LOGICe; GE Healthcare, München, Germany) and calculated as $1/3(v_{systolic} + 2v_{diastolic})$. Cerebrovascular resistance (CVR) was calculated as MAP/MFV.

Fractional tissue oxygen extraction and MFV were assessed 1 h before and 1 h after the sedation switch, because this relatively short time window allowed ventilatory settings and systemic parameters to be kept mostly unchanged, and were measured bilaterally. In cases where only a signal from one side was available, this was then used; in cases where the lesion was bilateral or diffuse, the mean of the bilateral values was used for further analysis. Systemic oxygenation values were also assessed 1 h before and after the sedation switch. ICP, MAP and CPP were measured hourly from 6 h before to at least 12 h after the sedation switch. In-house standard operating procedures for analgosedation, ventilator weaning, transfusion (target hemoglobin >8 g/dl in all patients), normothermia, ventilation, MAP/CPP and ICP management were used. We predefined critical values as follows: SaO_2 <90 %, $ScvO_2$ <70 %, rSO_2 <50 % or 20 % decrease from baseline, ICP >25 mmHg, MAP <80 mmHg and CPP <60 mmHg.

Statistical analysis

The recorded parameters were analyzed descriptively. According to the scale level of the variables, means and standard deviations or absolute and relative frequencies are given. Measurements before and after the switch were compared using the Student's t test for paired data. p values were considered significant if >0.05 but descriptive and no adjustment for multiple comparisons was made. Explorative analysis of subgroup differences was done by repeated measures analysis of variance with time as the within-subject factor and diagnosis (or sedation) as the between-subject factor. All analyses were done using Windows Excel for data handling and IBM SPSS Statistics 19 for further statistics.

Results

Patients

During the study period, 742 patients were admitted to our NICU, 146 of whom were equipped with multimodal neuromonitoring, and 132 of whom were ventilated for more than 24 h. Of these patients, 72 were recruited for other interventional trials. Of the remaining 60 patients, 41 either were not cerebrovascular or met other exclusion criteria (see above), leaving 19 patients for recruitment. Therefore, 19 consecutive patients with the admission diagnoses of severe IS (3), SAH (4) or ICH (12) were included, many of whom deteriorated early after admission. The demographic, clinical and sedation details of the included patients are summarized in Table 1. Sedation was induced with propofol in 12 patients and with midazolam (because of propofol-induced hypotension/bradycardia) in 7; initially, 1 patient was directly started on isoflurane. Patients were switched to isoflurane for a mean of 3.5 days (individual durations are shown in Table 1). Sufficient depth of sedation (RASS score before and after the switch −4 to −5) was achieved in most patients by isoflurane alone at concentrations ranging from MAC 0.5 to 0.8 (Table 3). In four patients, however, each previous intravenous sedation could not be completely stopped within 1 h, but had to be continued at a reduced rate for an overlapping period of another 1–2 h.

Adverse effects

No relevant overt safety concerns for patients or staff and no complications (such as malignant hyperthermia) emerged during or after the use of isoflurane. No liver enzyme increases or renal impairment related solely to isoflurane were detected. An autopsy in one patient did not show neuropathological abnormalities other than those associated with the admission diagnosis. Two patients developed anisocoria without changes in ICP or on a control CT scan that disappeared after cessation of isoflurane. In two patients, volatile sedation was stopped earlier than planned because of suboptimal gas resorption due to severe bronchial secretions or because of emergence of relevant intrapulmonary shunts.

Short-term observations (1 h before to 1 h after starting isoflurane)

Mean ICP showed an absolute increase of 2.1 mmHg ($p = 0.1$, Table 2). Mean MAP and CPP both decreased after initiation of isoflurane by 6.5 mmHg ($p = 0.076$) and 6.3 mmHg ($p = 0.119$), respectively (Fig. 1; Table 2) despite counteracting measures (see below).

Table 1 Baseline demographic and clinical patient characteristics

Patient no.	Age (years)	Sex	Diagnosis	Features	NIHSS scale score on admission	Modified Rankin scale score		ICU length of stay (days)	Volatile sedation duration (days)	Died on ICU
						Before admission	On admission			
1	69	Male	ICH	ICH volume 10 ml; IVH, G 8	38	0	5	11	6	Yes
2	52	Female	ICH	ICH volume 65 ml; IVH, G 6	38	0	5	18	2	No
3	69	Male	ICH	IVH G 5	5	0	2	24	5	No
4	49	Male	ICH	ICH volume 17 ml	13	0	3	19	11	Yes
5	82	Male	ICH	ICH volume 39 ml; IVH, G 6	18	3	5	8	3	Yes
6	74	Female	ICH	ICH volume 79 ml; IVH, G 8	18	0	5	12	6	No
7	63	Female	ICH	ICH volume 4 ml; IVH, G 2	17	1	5	18	1	No
8	84	Male	ICH	ICH volume 4 ml; IVH, G 6	5	2	4	16	7	No
9	85	Male	ICH	ICH volume 23 ml; IVH, G 10	18	0	5	14	5	No
10	65	Female	ICH	ICH volume 19 ml; IVH, G 6	19	0	4	18	1	No
11	76	Male	ICH	IVH, G 11	20	0	5	18	2	No
12	56	Male	ICH	ICH volume 40 ml	20	0	5	29	1	No
13	43	Male	SAH	IVH, G 10, HH 3, F 3	1	0	5	7	1	Yes
14	65	Female	SAH	IVH, G 10, HH 3, F 2	3	0	2	10	2	Yes
15	62	Female	SAH	HH 5; F 3	35	0	4	24	4	No
16	55	Male	SAH	HH 5; F 3	38	2	5	14	2	Yes
17	78	Male	IS	1/3 MCA, ICH, IVH	12	1	5	30	2	No
18	75	Male	IS	2/3 MCA, ICH, IVH	8	0	5	33	5	No
19	80	Female	IS	Cerebellar	30	1	5	4	1	Yes

ICH intracerebral hemorrhage, *SAH* subarachnoid hemorrhage, *IS* ischemic stroke, *MCA* middle cerebral artery, *IVH* additional intraventricular hemorrhage, *NIHSS* National Institute of Health Stroke Scale, *HH* Hunt and Hess score, *G* Graeb score, *F* Fisher scale score

Table 2 Short-term changes in systemic and cerebral monitoring parameters

Parameter	Hemisphere	1 h before switch	1 h after switch	Difference		*p* value
		Mean ± SD	Mean ± SD	Mean ± SD	95 % CI	
ICP (mmHg)	n.a.	5.13 ± 5.21	7.27 ± 7.43	2.13 ± 4.69	−0.46 to 4.73	0.100
MAP (mmHg)	n.a.	83.25 ± 14.73	76.75 ± 12.48	−6.50 ± 13.66	−13.78 to 0.78	0.076
CPP (mmHg)	n.a.	77.67 ± 16.74	71.40 ± 10.60	−6.27 ± 14.60	−14.35 to 1.82	0.119
MCA MFV (cm/s)	Affected	51.86 ± 23.00	57.01 ± 19.70	5.15 ± 16.31	−4.27 to 14.57	0.259
	Non-affected	51.56 ± 23.41	54.38 ± 20.67	2.81 ± 18.81	−7.21 to 12.84	0.559
SaO_2 (%)	n.a.	97.06 ± 1.89	97.47 ± 1.66	0.41 ± 2.09	−0.66 to 1.49	0.429
$ScvO_2$ (%)	n.a.	77.47 ± 8.46	81.59 ± 5.46	4.12 ± 4.76	1.67 to 6.56	0.003*
rSO_2 (cm/s)	Affected	70.74 ± 7.39	74.76 ± 4.98	4.03 ± 5.62	1.14 to 6.92	0.009*
	Non-affected	72.18 ± 6.29	76.71 ± 6.51	4.53 ± 5.92	1.49 to 7.57	0.006*
$SaO_2 - rSO_2$ (%)	Affected	26.32 ± 7.35	22.71 ± 5.08	−3.62 ± 5.90	−6.65 to −0.59	0.022*
	Non-affected	23.53 ± 5.06	20.18 ± 6.69	−3.35 ± 6.15	−6.52 to −0.19	0.039
$SaO_2 - ScvO_2$ (%)	n.a.	19.59 ± 7.84	15.88 ± 4.78	−3.71 ± 4.97	−6.26 to −1.15	0.007*
FTOE	Affected	0.27 ± 0.08	0.23 ± 0.05	−0.04 ± 0.06	−0.07 to −0.01	0.018*
	Non-affected	0.24 ± 0.05	0.21 ± 0.07	−0.04 ± 0.06	−0.07 to 0.00	0.031*
$PaCO_2$ (mmHg)	n.a.	38.06 ± 2.36	39.77 ± 3.10	1.71 ± 4.53	−1.77 to 5.19	0.290
CVR MAP/MCAvm (mmHg/cm/s)	n.a.	1.71 ± 0.67	1.54 ± 0.65	−0.17 ± 0.68	−0.58 to 0.24	0.384

A full dataset was obtained in 16 patients, data on ICP (and thus CPP) were missing in 1 patient, MFV in 2 patients, and FTOE in 2 patients (partially overlapping) for various technical reasons

ICP intracranial pressure, *MAP* mean arterial pressure, *CPP* cerebral perfusion pressure, *MCA MFV* middle cerebral artery mean flow velocity, *SaO_2* arterial blood oxygen saturation, *$ScvO_2$* central venous oxygen saturation, *rSO_2* regional cerebral tissue oxygen saturation, *FTOE* fractional tissue oxygen extraction (= (SaO_2−rSO_2)/SaO_2), *$PaCO_2$* partial arterial pressure of CO_2, *CVR* cerebrovascular resistance (= MAP/MCA MFV), *n.a.* not applicable

* $p < 0.05$, paired *t* test

There were no relevant changes in mean MFV, $PaCO_2$ (a determinant of cerebral vasoreactivity), or CVR. Oxygen saturation did not change; however, increasing $ScvO_2$ and rSO_2 led to reductions in systemic ($SaO_2 - ScvO_2$) and cerebral ($SaO_2 - rSO_2$) arteriovenous differences. Due to the latter, mean FTOE also decreased from 0.24 before to 0.21 after the switch (95 %CI −0.07 to 0.00; $p = 0.031$; Fig. 1; Table 2).

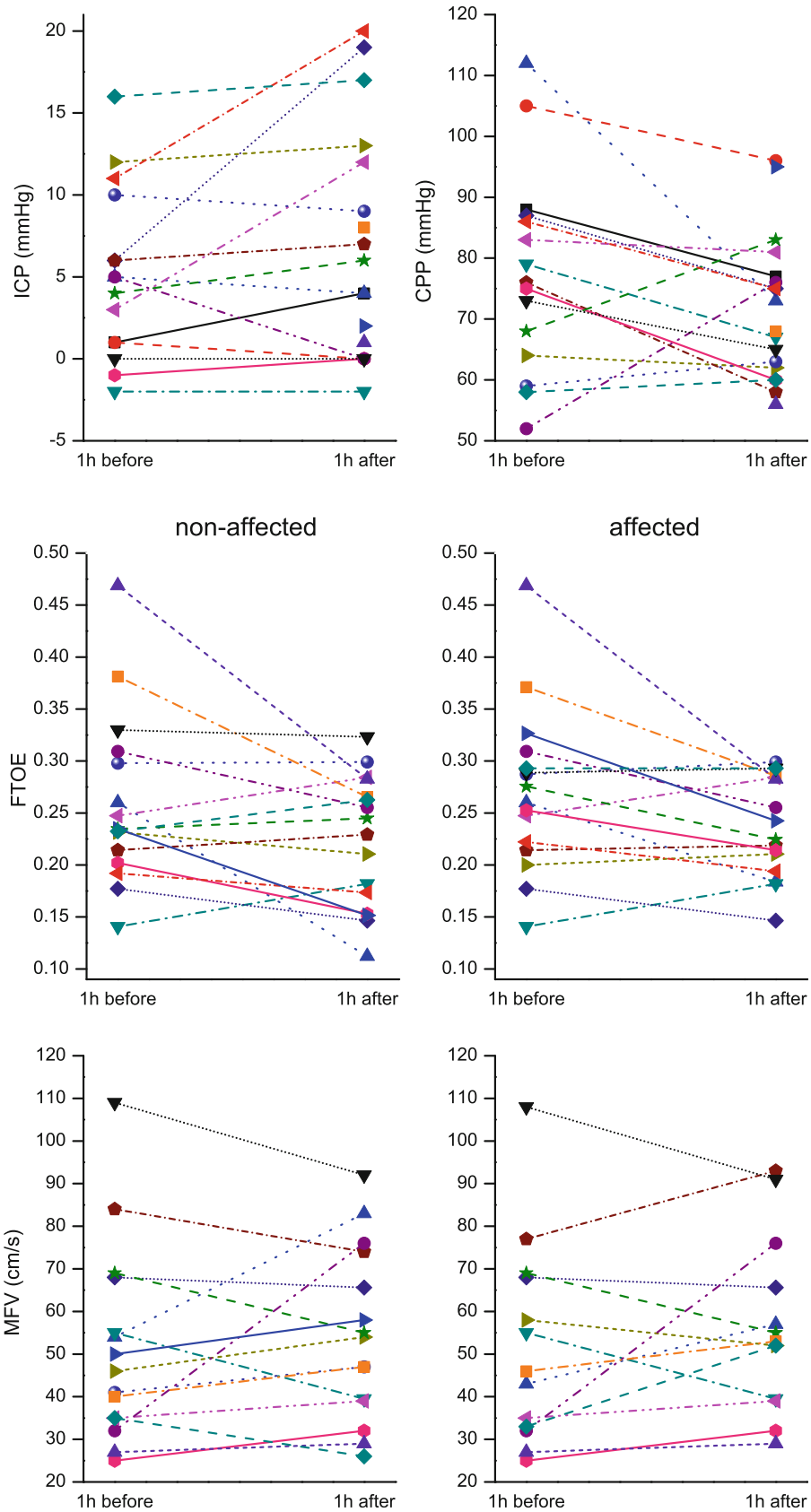

Fig. 1 Individual changes in ICP, CPP, MFV and FTOE 1 h before and 1 h after the sedation switch to isoflurane for each non-affected and affected hemisphere (for FTOE and MFV). A full dataset was obtained in 16 patients, data were missing for ICP (and thus CPP) in 1 patient, MFV in 2 patients, and FTOE in 2 patients (partially overlapping) for various technical reasons

Long-term observations (6 h before to 12 h after starting isoflurane)

Changes in the mean values from the pre-start phase (−6 to −1 h) to early (+1 to +6 h) and late (+6 h to +12 h) phases after starting are given in Table 3. ICP remained stable, without necessary additional osmotherapy or augmentation of CSF drainage by EVD. Although MAP was counterbalanced by vasopressors, mean CPP decreased by 9.9 mmHg in the early phase and by 7.5 mmHg in the late phase (Fig. 2). To detect potential differences in pressure dynamics, the three disease entities were also analyzed separately. This did not reveal great deviations from the behavior of the whole group, particularly regarding patients with ICH and SAH. The three patients with IS, however, showed a more pronounced decrease in MAP and thus CPP, and a decrease, as opposed to a slight increase (ICH/SAH), in ICP at 6 and 12 h (see Electronic supplementary material). ICP dynamics were similar in those with previous propofol sedation and those with midazolam sedation, while MAP/CPP decreases appeared more pronounced in the latter (see Table S2a Electronic supplementary material).

Peak and mean inspiratory pressures, and thus minute volume, were increased over time to achieve constant oxygenation (PaO_2/FiO_2). In spite of this, $PaCO_2$ showed an increase and thus pH showed a decrease over the long term, both significant (Table 3; Fig. 2). In terms of drug administration, remifentanil and sufentanil could be reduced. However, noradrenaline concentrations constantly increased with increasing MAC of isoflurane (Fig. 2), and had to be significantly increased about 1.5-fold in both phases after the sedation switch to keep MAP and CPP above tolerable thresholds.

Discussion

Isoflurane at effective sedation doses did not compromise cerebral oxygenation (short-term), blood flow (short-term) or ICP (short-term and long-term) to clinically relevant extents. However, it led to considerable depression of CPP that required substantial counteracting with vasopressors.

In addition to acknowledged general advantages of isoflurane as an anesthetic, it has shown neuroprotective effects when used prior to (preconditioning) [22, 23] or during [24, 25] ischemic insults in a considerable number of experimental studies [7]. Supportive clinical reports are scarce and limited to short-term use during surgery [26, 27]. Long-term administration in neurocritical care was hardly feasible until the advent of AnaConDa®, although there is an early report comparing isoflurane with midazolam for ICU sedation, without detection of adverse effects [28]. In two cases, prolonged use in the NICU via an OR respirator in refractory status epilepticus resulted in effective control of seizure activity but did not convincingly improve outcome [29] and possibly caused basal ganglia MRI abnormalities [9]. Recent experimental studies have even suggested neurotoxic effects including apoptosis induction [8] and amyloid deposition [30]. The greatest concerns are based on OR studies that have shown increases in ICP [10, 11, 15, 16] through isoflurane-associated cerebral vasodilation [12, 13]. Although other studies have not confirmed these findings [31, 32], sedation with isoflurane is currently off-label and discouraged in brain-injured patients who are prone to ICP elevations.

In our study, we did not detect relevant short-term changes in MFV after starting isoflurane. Thus, a direct vasodilatory effect was neither directly observed nor indirectly suggested by a compensatory decrease in CVR (which was absent in the short term). Possibly, the dose-dependent [16, 33] effect might not have been relevant at our sedation doses, which were considerably lower than in the OR setting. Alternatively, vasodilation might have occurred later in the course and was thus not picked up during the momentary measurement 1 h after the sedation switch when residual effects of the potential rCBF depressors propofol and midazolam might have been present. Finally, it might be more revealing to assess peripheral vasodilation in the microcirculation, rather than at the level of the MCA main stem. Recently in 13 patients with SAH equipped with a thermal diffusion probe and transtemporal duplex/Doppler sonography who were switched from propofol to isoflurane, no change in MCA transcranial Doppler velocity was found, but a significant increase of rCBF was found in the microcirculation [34].

The absence of proximal vasodilation might explain why we observed only slight increases in individual ICP values under isoflurane, but not to a clinically relevant extent. Of note, ICP was not externally influenced by measures such as osmotherapy, and thus probably reflects spontaneous fluctuations. It cannot be ruled out, however, that our active measures to control MAP in some cases may have influenced ICP, as is observed in impaired cerebral autoregulation.

MAP was reduced by isoflurane regardless of the underlying disease entity or previous sedation type, with minor differences in the extent. That this decrease appeared more pronounced in patients treated with midazolam than in those treated with propofol probably relates to previous MAP depression by propofol, hence resulting in a smaller difference to the subsequent isoflurane-induced depression. CPP was therefore considerably affected and had to be actively raised by additional noradrenaline. This was not associated with overt side effects here, but potentially exposes the patient to tachyarrhythmia, gastrointestinal disturbance or

Table 3 Long-term parameter changes after the sedation switch to isoflurane

Parameter	Baseline before switch		After switch											
	−6 to −1 h		+1 to +6 h							+7 to +12 h				
	Mean	SD	Mean	SD	Difference from baseline					Mean	SD	Difference from baseline		
					Mean	SD	95 % CI	*p* value	Mean			SD	95 % CI	*p* value
Cerebral (mmHg)														
ICP	5.40	4.79	6.45	5.42	1.05	3.59	−0.73 to 2.84	0.230	6.75	5.85	1.36	3.73	−0.50 to 3.21	0.141
CPP	83.11	10.28	73.17	9.75	−9.93	9.40	−14.61 to −5.26	≤0.001*	75.60	10.47	−7.51	9.78	−12.37 to −2.64	0.005*
Cardiovascular														
Heart rate (min^{-1})	66.88	14.64	72.16	16.41	5.28	10.58	0.18 to 10.38	0.043*	72.31	13.55	5.43	14.63	−1.62 to 12.48	0.123
MAP (mmHg)	86.79	10.42	79.05	8.88	−7.74	10.18	−12.80 to −2.67	0.005*	81.32	8.71	−5.47	10.12	−10.50 to −0.44	0.035*
Fluid input (ml/h)	187.76	48.92	191.83	73.29	4.07	61.39	−25.52 to 33.66	0.776	189.74	90.66	1.97	93.20	−42.95 to 46.89	0.927
Fluid output (ml/h)	144.42	65.45	143.06	64.06	−1.36	83.88	−41.79 to 39.07	0.944	144.98	88.39	0.56	107.40	−51.20 to 52.33	0.982
Respiratory														
Respiratory rate (min^{-1})	13.21	2.67	14.06	3.29	0.86	2.80	−0.49 to 2.21	0.198	14.24	2.89	1.04	2.60	−0.22 to 2.29	0.100
Minute volume (l/min)	6.63	1.54	7.24	1.58	0.61	0.95	0.16 to 1.07	0.011*	7.73	1.75	0.99	1.08	0.46 to 1.53	≤0.001*
PaO_2/FiO_2	262.44	74.82	268.81	77.45	6.37	37.36	−11.64 to 24.38	0.467	272.34	77.30	9.91	38.36	−8.58 to 28.39	0.275
FiO_2 (%)	41.69	11.00	41.12	8.56	−0.57	9.21	−5.01 to 3.87	0.790	40.44	8.46	−1.25	9.57	−5.86 to 3.36	0.576
$PaCO_2$ (mmHg)	36.71	5.69	41.38	4.75	4.67	4.35	2.57 to 6.76	≤0.001*	40.40	5.00	3.69	5.24	1.17 to 6.21	0.007*
PEEP (cmH_2O)	6.74	2.26	7.01	2.25	0.27	1.20	−0.31 to 0.84	0.341	7.32	2.16	0.58	1.27	−0.04 to 1.19	0.063
P_{peak} (cmH_2O)	19.46	3.49	20.94	4.05	1.48	2.00	0.52 to 2.45	0.005*	21.81	4.33	2.36	2.22	1.28 to 3.43	≤0.001*
P_{mean} (mbar)	11.02	3.22	12.18	3.48	1.17	1.95	0.23 to 2.11	0.018*	12.51	3.43	1.49	1.41	0.81 to 2.17	≤0.001*
Drugs														
Isoflurane (MAC)			0.56	0.12					0.68	0.13				
Propofol (mg/kg/h)	2.69	1.34	0.22	0.41	−2.46	1.14	−3.15 to −1.78	≤0.001*	0.00	0.00	−2.69	1.34	−3.50 to −1.88	≤0.001*
Midazolam (mg/kg/h)	0.22	0.04	0.02	0.02	−0.19	0.06	−0.25 to −0.14	≤0.001*	0.00	0.00	−0.22	0.04	−0.25 to −0.18	≤0.001*
Remifentanil (μg/kg/min)	0.11	0.05	0.07	0.04	−0.03	0.04	−0.07 to 0.00	0.046*	0.05	0.06	−0.06	0.06	−0.10 to −0.01	0.021*
Sufentanil (μg/kg/h)	0.81	0.58	0.65	0.40	−0.17	0.41	−0.40 to 0.07	0.144	0.73	0.29	−0.08	0.50	−0.37 to 0.21	0.564
Noradrenaline (μg/kg/min)	0.11	0.09	0.15	0.10	0.04	0.06	0.01 to 0.08	0.008*	0.17	0.11	0.06	0.07	0.03 to 0.10	0.002*

ICP intracranial pressure, *CPP* cerebral perfusion pressure, *MAP* mean arterial pressure, PaO_2 partial pressure of arterial oxygen, FiO_2 fraction of inspired oxygen, $PaCO_2$ partial pressure of arterial CO_2, *PEEP* positive end-expiratory pressure, P_{peak} peak inspiratory pressure, P_{mean} mean inspiratory pressure, *MAC* minimal alveolar concentration
*$p < 0.05$, paired *t* test

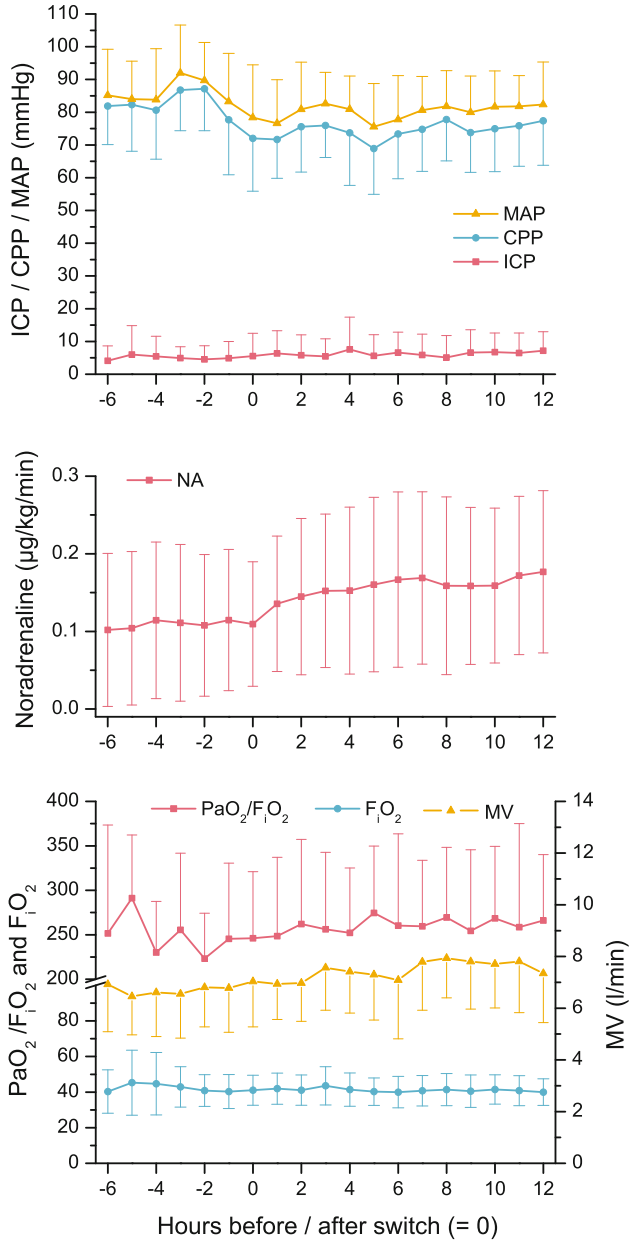

Fig. 2 Dynamics of selected mean values from 6 h before to 12 h after the switch of sedation to isoflurane (hourly means and standard deviations). *ICP* intracranial pressure, *MAP* mean arterial pressure, *CPP* cerebral perfusion pressure, *NA* infusion rate of noradrenaline, PaO_2 partial pressure of arterial oxygen, FiO_2 fraction of inspired oxygen, *MV* minute volume

impairment of the microcirculation. Opioids could be reduced under isoflurane, reflecting its partial analgesic component.

Isoflurane significantly decreased cerebral and systemic oxygen extraction, which might reflect isoflurane's well-known ability to reduce the metabolic rate and thus cerebral and systemic oxygen consumption. A comparable cerebral metabolic rate/O_2-reducing effect of isoflurane has been demonstrated in the (neuro)surgical OR setting [33, 35], but not in cerebrovascular ICU patients on the AnaConDa® system, so far. The observation that FTOE bihemispherically decreased in more than two-thirds of patients appears beneficial with regard to the risk of secondary ischemic damage and high oxygen demand in this patient population. However, the alternative that FTOE reduction might reflect a regional vascular steal effect cannot be ruled out in this study design, even though our results do not support a gross interhemispheric steal.

Liver enzymes and renal parameters were not adversely affected by isoflurane alone. We did not measure fluoride, a potentially nephrotoxic accumulative product of the metabolism of volatile sedatives, but isoflurane produces much less fluoride than sevoflurane, and the latter was recently investigated in a long-term study (7 days) of AnaConDa® ICU sedation and resulted in no renal impairment [5]. In terms of neurotoxicity, one single neuropathological work-up revealed no signs of basal ganglia injuries [9]. Intrapulmonary shunt in two patients was probably caused by blunting of hypoxic pulmonary vasoconstriction that is more common with isoflurane than with propofol [36]. The invasiveness of ventilation was slightly increased over the observation period, probably to compensate for the increase in dead space and CO_2 recycling [37] associated with the AnaConDa® device, but did not completely prevent a small long-term rise in $PaCO_2$ (and thus fall in pH), another point of concern in NICU patients with vascular disease. This underlines the importance of tightly controlling $PaCO_2$ when applying volatile sedation with the AnaConDa®. Finally, the atypical occurrence of anisocoria in two patients, not attributable to ICP crises and vanishing after isoflurane cessation, led to substantial alarm and unnecessary transports for CT scanning. Suggested mechanisms with other volatile agents are local pupillomotor effects and dysregulation of sympathetic tone [38].

Our study had several limitations. Above all, it was not a randomized comparison of isoflurane with an alternative sedative to test a hypothesis. Thus, no confirmatory analysis was planned and the reported *p* values are descriptive only. The patient sample was small and the vascular pathologies quite heterogeneous in nature, location, distribution and extension, thus possibly resulting in considerable differences in cerebral hemodynamic behavior. Given the fact that the majority of patients had ICH, our findings might mainly be applicable to hemorrhagic stroke and not to cerebrovascular disease in general. The chosen time-frames of the observation periods were arbitrary and might not have revealed all conceivable effects of isoflurane. While the short-term observation period allowed fairly good control of most management measures (and was therefore chosen for the more vulnerable measurements by TCD and NIRS), the long-term window was certainly more prone to uncontrollable

influences on physiology. Sedation level was assessed by the clinical score RASS only, and although this had been demonstrated to correlate well with bispectral index monitoring (BIS XP) in NICU patients [39], it would have been preferable to have employed more objective means of sedation monitoring in our study, too.

Excluding patients with high initial ICP values from the study was deemed ethically mandatory, but this might have created a caveat with regard to interpretation of our findings, further limiting generalizability and warranting caution. Residual effects of the previously administered sedatives and variations in the opioid dosing during the protocol cannot be ruled out. Finally, neuromonitoring has its own limitations: ICP values can differ considerably with different ways of measurement (e.g., EVD vs. tissue probe), MFV is a useful surrogate for rCBF in healthy subjects, but correlations are weaker in specific brain pathologies [40], and NIRS assesses a tiny frontal cortical area, while oxygenation effects close to the site of lesion might have been more relevant.

Still, this is to our knowledge the first prospective study of AnaConDa®-driven isoflurane sedation in stroke patients under invasive and non-invasive neuromonitoring, generating a considerable amount of novel data. And despite all the warranted caution suggested by our findings, we continue to consider isoflurane a potentially useful alternative for NICU sedation, provided neuromonitoring is in place. Selected patients with good systemic circulatory stability but compromised cerebral microcirculation (e.g., vasospasms in SAH, ischemic penumbra in large vessel occlusion IS) might benefit from volatile sedation. Transient application of isoflurane might provide the reported protective "preconditioning" effect to ameliorate secondary ischemia without risking neurotoxicity potentially associated with longer-term application.

Conclusions

In summary, our findings in this small and selected study population suggest that cerebrovascular NICU patients can be sufficiently sedated with isoflurane administered via an AnaConDa® device, in association with reductions in cerebral oxygen extraction and without relevant increases in ICP, if baseline ICP values are low or only moderately elevated. However, the observation of substantial MAP/CPP reductions and other adverse effects are concerning and warrant caution in this off-label treatment. We strongly recommend neuromonitoring in these patients. More confirmatory research in larger populations is clearly necessary before potential cerebral benefits of volatile sedation can be safely investigated.

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