S(+)-ketamine/propofol maintain dynamic cerebrovascular autoregulation in humans

[Une combinaison de S(+)-kétamine et de propofol maintient l'autorégulation vasculaire cérébrale dynamique chez l'humain]

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Purpose: This study investigates the effects of S(+)-ketamine and propofol in comparison to sevoflurane on dynamic cerebrovascular autoregulation in humans.

Methods: Twenty-four patients were randomly assigned to one of the following anesthetic protocols: group I (n=12): 2.5 mg·kg⁻¹·hr⁻¹ S(+)-ketamine, 1.5–2.5 µg·mL⁻¹ propofol-target plasma concentration; group II (n=12): 2.0 MAC (4.0 %) sevoflurane. Patients were intubated and ventilated with O₂/air (PaO₂=0.33). Following 40 min of equilibration dynamic cerebrovascular autoregulation was measured and expressed as the autoregulatory index (ARI), describing the duration of cerebral hemodynamic recovery in relation to changes in mean arterial blood pressure. Statistics: Mann-Whitney U test (statistical significance was assumed when P < 0.05).

Results: Dynamic cerebrovascular autoregulation was intact in all patients with S(+)-ketamine/propofol anesthesia as indicated by an ARI of 5.4 ± 1.1. In contrast, dynamic cerebrovascular autoregulation was significantly delayed with 2.0 MAC sevoflurane (ARI=2.6 ± 0.7).

Conclusion: Dynamic cerebrovascular autoregulation is maintained with S(+)-ketamine/propofol-based total iv anesthesia. In contrast, 2.0 MAC sevoflurane delayed dynamic cerebrovascular autoregulation. This supports the use of S(+)-ketamine in combination with propofol in neurosurgical patients based on its neuroprotective potential along with maintained cerebrovascular physiology.

Objectif : Examiner les effets de la S(+)-kétamine et du propofol, comparés au sévoflurane, sur l'autorégulation vasculaire cérébrale dynamique chez l'humain.

Méthode : Vingt-quatre patients ont été répartis au hasard et ont reçu un des protocoles anesthésiques suivants : groupe I (n = 12) : 2,5 mg·kg⁻¹·h⁻¹ de S(+)-kétamine, une concentration plasmatique cible de

propofol de 1,5 - 2,5 µg·mL⁻¹ ; groupe II (n = 12) : 2,0 CAM (4,0 %) de sévoflurane. On a procédé à l'intubation et à la ventilation avec un mélange de O₂/air (PaO₂ = 0,33). Après un temps d'équilibre de 40 min, l'autorégulation vasculaire cérébrale a été mesurée et exprimée comme l'indice d'autorégulation (IAR), décrivant la durée de la récupération hémodynamique cérébrale en relation avec les modifications de la tension artérielle moyenne. Données statistiques : test U de Mann-Whitney (signification statistique avec P < 0,05).

Résultats : L'autorégulation vasculaire cérébrale dynamique était intacte chez tous les patients sous anesthésie avec S(+)-kétamine/propofol comme l'indiquait un IAR de 5,4 ± 1,1. Par ailleurs, elle a été significativement retardée avec les 2,0 CAM de sévoflurane (IAR = 2,6 ± 0,7).

Conclusion : L'autorégulation vasculaire cérébrale dynamique est maintenue avec une anesthésie exclusivement intraveineuse à base de S(+)-kétamine/propofol mais retardée avec 2,0 CAM de sévoflurane. Ces données favorisent l'usage de S(+)-kétamine combinée au propofol, en neurochirurgie, usage fondé sur leur potentiel de neuroprotection et de maintien de la physiologie vasculaire cérébrale.

ANESTHETIC drugs and their combinations suitable for use in neurosurgical patients require the following pre-requisites: (a) no elevation of intracerebral pressure (ICP); (b) maintenance of coupling between cerebral blood flow (CBF) and cerebral metabolism (CMR); (c) rapid recovery for immediate postoperative assessment; (d) neuroprotective potential; (e) intact cerebrovascular autoregulation.

The N-methyl-D-aspartate (NMDA)-receptor antagonist ketamine has never been considered to be an adequate drug in neurosurgical patients, primarily because of historical reports of elevated ICP following

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ketamine infusion. However, recent investigations showed that ketamine or its enantiomere S(+)-ketamine meets most of the above mentioned criteria: ketamine as a single anesthetic or in combination with benzodiazepines, propofol or isoflurane does not affect ICP¹⁻³ or the coupling between CBF and CMR.⁴ Likewise, recovery of postoperative psychomotor function and performance was more rapid with the enantiomere S(+)-ketamine compared to racemic ketamine.⁵ In animal models of cerebral ischemia and traumatic head injury ketamine and its enantiomere S(+)-ketamine showed brain protective potential even when administered one hour after the insult.⁶⁻⁸ Although cerebrovascular autoregulation in the rat was intact with S(+)-ketamine, it is unclear whether total *iv* anesthesia (TIVA) using S(+)-ketamine in combination with propofol affects cerebrovascular autoregulation in humans. Therefore the present study investigates the effects of S(+)-ketamine and propofol (a combination adequate to provide anesthesia during surgery) on the dynamic component of cerebrovascular autoregulation in comparison to sevoflurane anesthesia.

Methods

Following IRB approval, written informed consent was obtained in 24 patients (ASA physical status I–II) scheduled for elective abdominal surgery. Patients with a history of cardiac or cerebrovascular disease, diabetes, systemic vascular disorders, or the use of psychoactive drugs were excluded from the study. One hour prior to general anesthesia 3.75 mg midazolam was administered orally to the patients.

To assess dynamic cerebrovascular autoregulation the middle cerebral artery (MCA) blood flow velocity (CBFV) was measured by the transtemporal approach using a 2-MHz transcranial Doppler system (TCD, Multidop P, DWL, Sipplingen, Germany). To ensure constant angles of insonation the TCD-probe was fixed using a specially designed frame during the whole study. CBFV, invasive mean arterial blood pressure (MAP), and heart rate (HR) were monitored continuously.

To activate autoregulatory vasodilation a non-pharmacological sudden decrease in MAP of 15–20 mmHg was induced by rapid (<0.5 sec) deflation of large cuffs placed around both thighs, previously inflated to suprasystolic blood pressure levels for three minutes.^{9,10} With intact physiology the decrease in MAP is expected to recover within 30–40 sec, while CBFV (as an index of flow) returns to baseline values within five to ten seconds. The status of cerebrovascular autoregulation is expressed as the autoregulatory index (ARI), describing

the duration of CBFV recovery in relation to changes in MAP. The calculation of the ARI was performed off-line using the software program supplied by the TCD manufacturer (DWL, Sipplingen, Germany). This software program uses a previously validated algorithm based on a second-order linear differential equation calculating the best fit for the actual CBFV autoregulatory curve to one of ten hypothetical CBFV autoregulatory curves as described in the appendix.¹⁰ The slope of the autoregulatory curve increases with the speed of the autoregulatory response, both of which elevate the ARI. For example, any recovery of CBFV independent of MAP results in incremental steps of the CBFV curve and translates to an ARI of 4–6 indicating intact cerebrovascular autoregulation.¹¹ A pressure passive CBFV-pattern equals no difference between the CBFV and the MAP curve and translates to an ARI of 0 (=no autoregulation).

Patients were randomly assigned to one of the following anesthetic protocols. In group I ($n=12$) anesthesia was induced with 2.0 mg·kg⁻¹ S(+)-ketamine combined with a propofol-target plasma concentration of 3.0 µg·mL⁻¹ (Disoprifusor®, Master-TCI, Beckton Dickinson) and atracurium (Tracrium®, GlaxoWellcome, 0.5 mg·kg⁻¹). Patients were intubated and ventilated with O₂/air (PaO₂=0.33). Anesthesia was maintained with 2.5 mg·kg⁻¹·hr⁻¹ S(+)-ketamine combined with a propofol-target plasma concentration of 1.5–2.5 µg·mL⁻¹ (i.e., about 2.0–4.0 mg·kg⁻¹·hr⁻¹ propofol). In group II ($n=12$) anesthesia was induced with 1.5 µg·kg⁻¹ remifentanyl (Ultiva®, GlaxoWellcome, administered within 90 sec) and a propofol-target plasma concentration of 3.0 µg·mL⁻¹ and atracurium (0.5 mg·kg⁻¹). Following intubation, propofol infusion was terminated and patients were ventilated with 2.0 MAC sevoflurane end-tidal concentration (Sevorane®Abott, 4.0 %) in O₂/air (PaO₂=0.33). The operation was then started and the abdomen was opened. After this intense stimulus, surgery on the gastrointestinal tract began, which represents a very low and constant stimulus for the patient. During this period, at least 40 min after induction of anesthesia (equilibration time), dynamic cerebrovascular autoregulation was tested four times (one measurement every five minutes). Arterial blood gases and body temperature were maintained constant over time. MAP was supported with noradrenaline (1–5 µg·min⁻¹) when MAP decreased below 80 mmHg.

The mean of the four measurements was calculated for each variable and then compared between groups. Data are reported as mean ± SD. For statistical analysis comparison between groups was performed with the Mann-Whitney U test. A *P*-value of less than 0.05 was considered statistically significant.

TABLE I Patient characteristics

	<i>S(+)-ketamine/propofol</i> (group I; n=12)	<i>Sevoflurane</i> (group II; n=12)
Age (yr)	52 ± 11	52 ± 10
Weight (kg)	69 ± 14	73 ± 10
Sex (m/f)	7/5	5/7

No significant differences between groups. Data are presented as mean ± SD ($P < 0.05$).

TABLE II Physiologic variables during cerebral autoregulation tests (mean ± SD)

	<i>S(+)-ketamine/propofol</i> (group I; n=12)	<i>Sevoflurane</i> (group II; n=12)
MAP (mmHg)	100 ± 14	86 ± 8*
HR (beats·min ⁻¹)	70 ± 13	76 ± 17
CBFV (cm·sec ⁻¹)	40 ± 14	42 ± 9
PaCO ₂ (mmHg)	35 ± 2	35 ± 1
ARI	5.4 ± 1.1	2.6 ± 0.7*

MAP= mean arterial blood pressure; HR=heart rate; CBFV=cerebral blood flow velocity; ARI=autoregulatory index.

*=significantly different compared to group I ($P < 0.05$)

Results

There were no differences between groups regarding demographic data (Table I).

Table II shows the physiologic variables and the ARI in both groups. MAP was lower with sevoflurane anesthesia compared to patients anesthetized with S(+)-ketamine/propofol. The step decrease in MAP after deflation of the thigh cuffs was 21 mmHg in group I and 19 mmHg in group II. There were no differences in HR, mean CBFV, or arterial CO₂ concentration between groups. Dynamic cerebrovascular autoregulation was intact in patients anesthetized with S(+)-ketamine/propofol (ARI=5.4 ± 1.1, group I). In contrast, in patients anesthetized with 2.0 MAC sevoflurane (group II) ARI was decreased (2.6 ± 0.7; $P < 0.05$ compared to group I).

The Figure shows two representative recordings from dynamic cerebrovascular autoregulation measurement. Deflation of thigh cuffs produced a sudden decrease of MAP and CBFV. In patients anesthetized with S(+)-ketamine/propofol (Figure a) CBFV returned to baseline in less than ten seconds while MAP did not reach baseline-level within 30 sec, indicating intact dynamic cerebrovascular autoregulation. In patients with 2.0 MAC sevoflurane (Figure b) recovery of CBFV was delayed.

FIGURE Representative recordings of the dynamic cerebrovascular autoregulation tests in two patients anesthetized with either (a) S(+)-ketamine/propofol or (b) 2.0 MAC sevoflurane (↓=release of thigh cuffs; MAP=mean arterial blood pressure; CBFV=cerebral blood flow velocity).

Discussion

CBF autoregulation may be assessed in relation to its static and dynamic regulatory components. While static autoregulation describes the qualitative potential of cerebral vessels to regulate for changes in cerebral perfusion pressure, dynamic autoregulation represents the immediate response of autoregulatory vasomotion. It is generally believed that static autoregulation is always intact as long as the dynamic component is not impaired. However, dynamic autoregulation may be altered without concomitant changes in static

autoregulation.^{9,10} This indicates that the dynamic component appears to be more sensitive to physiological or pathophysiological challenges.

The effects of racemic ketamine or S(+)-ketamine on CBF are still controversial. *In vitro* studies have shown that racemic ketamine dilates cerebral arteries by suppression of the release of the vasoconstrictive compound endothelin or by acting as a calcium channel blocker of both potential-operated and receptor-operated channels in cerebrovascular smooth muscle.¹²⁻¹⁴ This is consistent with studies in awake or N₂O/O₂-ventilated animals and humans where racemic ketamine increased CBF along with increases in MAP.^{15,16} In contrast, in the presence of anesthetics depressing cerebral metabolism, ketamine did not change or decrease CBF.^{1,17,18} This suggests that the effect of ketamine on CBF is related to the pre-existing cerebrovascular tone induced by the background anesthetic technique. However, it is also possible that changes in CBF occur secondary to changes in MAP (i.e., impaired cerebrovascular autoregulation).^{15,16}

The present investigation shows that S(+)-ketamine in combination with low-dose propofol did not alter the dynamic cerebrovascular response to a decrease in MAP. As propofol in concentrations used in the present study does not influence cerebrovascular autoregulation,⁹ the present data suggest that S(+)-ketamine does not influence dynamic and static autoregulation. Likewise, static cerebrovascular autoregulation was generally maintained in S(+)-ketamine-anesthetized rats.¹⁹ However, low doses of S(+)-ketamine (0.5 mg·kg⁻¹·min⁻¹) shifted the autoregulatory curve towards higher MAP values, an effect that is likely related to elevated sympathetic tone of cerebral vessels.^{7,19} Increasing the dose of S(+)-ketamine (1.0 mg·kg⁻¹·min⁻¹) reversed this effect along with a decrease in plasma-catecholamine concentrations. These data suggest that changes in CBF seen in historical studies are unlikely related to impaired CBF autoregulation in humans and animals.

Several studies investigated the effects of sevoflurane on cerebrovascular autoregulation. In humans sevoflurane concentrations 1.5 MAC did not affect static cerebrovascular autoregulation.²⁰⁻²² However, studies in rats have shown that higher concentrations of sevoflurane (2.0 MAC) impair static cerebrovascular autoregulation in a fashion similar to other volatile anesthetics.²³ The dynamic component of cerebrovascular autoregulatory response, which appears to be a more sensitive indicator of altered physiology than the static component, was intact with 1.5 MAC sevoflurane,²⁴ but delayed with 2.0 MAC sevoflurane during the present investigation. This suggests a threshold

effect for volatile anesthetics on the cerebral vasculature. It is unclear by which mechanism volatile anesthetics prolong the time necessary for dynamic autoregulatory vasodilation. The immediate temporal profile of dynamic cerebrovascular autoregulation (within one to ten seconds upon cuff release) indicates a very fast acting mechanism, possibly involving an increased concentration of nitric oxide (NO) or an increased sensitivity of the vascular smooth muscle to normal concentrations of NO.²⁵

Studies in humans have shown that ARI is constant in the order of 5 ± 1 in neurologically healthy, awake patients.^{11,24} The patients studied in the present investigation did not present with a medical history or clinical signs of cerebrovascular disease. We, therefore, assumed intact autoregulation in these patients and baseline measurements in awake patients were considered avoidable in order to reduce the preoperative psychological strain. During sevoflurane anesthesia (group II) noradrenaline (1–5 µg·min⁻¹) was necessary to maintain MAP within the autoregulatory range. Clinical and experimental studies indicate that the infusion of low concentrations of noradrenaline (<6 µg·min⁻¹) do not affect CBF as long as the blood-brain-barrier is intact.^{26,27} Despite infusion of noradrenaline, MAP was lower in patients receiving 2.0 MAC sevoflurane (group II). However, MAP was still within the autoregulatory range during measurements and differences in ARI between patients anesthetized with S(+)-ketamine/propofol or sevoflurane cannot be explained by differences in MAP. Although a blinded study protocol was not possible, the bias of the investigator is estimated to be minimal, as time intervals for inflation, duration and deflation of thigh cuffs are standardized and the ARI is automatically calculated by the computer.

In conclusion, S(+)-ketamine in combination with low doses of propofol did not affect dynamic cerebrovascular autoregulation. In this respect S(+)-ketamine appears to be suitable for neurosurgical patients, particularly with regard to the neuroprotective potential of this compound. In contrast, 2.0 MAC sevoflurane delays but does not abolish the autoregulatory response to a decrease in MAP.

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APPENDIX

Dynamic cerebrovascular autoregulation was calculated by the computer in steps of 100 msec using the following algorithm (second order linear differential equation).¹⁰

$$dP = (MAP - cABP) / (cABP - CCP)$$

$$x2 = x2 + (x1 - 2D \cdot x2) / (f \cdot T)$$

$$x1 = x1 + (dP - x2) / (f \cdot T)$$

$$mV = cVmca \cdot (1 + dP - K \cdot x2)$$

dP=normalized change in MAP (induced by cuff release)

cABP=control value of MAP (before cuff release)

CCP=critical closing pressure (calculated by the computer)

x1 and x2=state variables which were assumed to be equal to 0 during the control period

D=the damping factor

f=sampling rate (10Hz)

T=the time constant

mV=mean velocity

cVmca=control velocity in the middle cerebral artery (before cuff release)

K=the autoregulatory dynamic gain

These parameters were related to the dynamic autoregulatory index (ARI).