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Racemic ketamine does not abolish cerebrovascular autoregulation in the pig

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Background: Little is known about the influence of racemic ketamine on autoregulation of cerebral blood flow (CBF), and available reports regarding its influence on cerebral hemodynamics are contradictory. This study was designed to evaluate cerebrovascular responses to changes in the mean arterial pressure (MAP) during ketamine anesthesia.
Methods: In eight normoventilated pigs anesthesia was induced with propofol and maintained by i.v. infusion of ketamine ($15.0\,mg\,kg^{-1}.h^{-1}$) during measurements. The intra-arterial xenon clearance technique was used to calculate CBF. Balloon-tipped catheters were introduced in the inferior caval vein and mid-aorta, and increases or decreases by up to 40% in mean arterial pressure (MAP) in random order were achieved by titrated inflation of these balloon catheters. Cerebral blood flow was determined at each MAP level. Regression coefficients of linear pressure-flow curves were calculated in all animals.
Results: From the mean baseline level (101 mmHg) MAP was reduced by 20% and 40%, and increased by 26% and 43%. The maximal mean increase and decrease in MAP induced a 12% increase and a 15% decrease, respectively, of CBF from the mean baseline level ($52.6\,ml.100\,g^{-1}.min^{1}$). The 95% confidence interval (-0.02; 0.38) of the mean regression coefficient of individual pressure-flow curves does not include the regression coefficient (0.64) of a linear correlation between MAP and CBF including origo (correlation coefficient 0.99), which indicates complete lack of cerebrovascular autoregulation.
Conclusions: We conclude that autoregulation of CBF is not abolished during continuous ketamine infusion in normoventilated pigs and that previous divergent conclusions are unlikely to be associated with severe impairment of cerebrovascular autoregulation.

Racemic ketamine is a non-competitive N-methyl-D-aspartate receptor antagonist containing equal proportions of the two enantiomers S-(+)- and R-(–)-ketamine. Despite its unique analgesic, anesthetic and hemodynamic properties, little is known about the influence of racemic ketamine on autoregulation of cerebral blood flow (CBF). Available reports on cerebral hemodynamic effects of ketamine (1–7) are contradictory. Impairment of cerebrovascular autoregulation by ketamine might partly explain these diverging findings.

To date no systematic study regarding the effects of racemic ketamine on cerebral autoregulation is available. The present study was undertaken to evaluate CBF responses to different mean arterial pressure (MAP) levels induced non-pharmacologically during i.v. infusion of racemic ketamine.

Materials and methods

The experiments were carried out at the Department of Experimental Research, Malmö University Hospital, after approval of the study design by the Medical Ethics Committee on Animal Studies, Lund University, Malmö, Sweden.

Animals
Eight juvenile domestic pigs (Swedish landrace/Yorkshire/Hampshire) were used. The animals were kept in laboratory stables and deprived of food overnight but had free access to water.

Anesthesia
Anesthesia was induced with i.v. propofol $4–6\,mg\,kg^{-1}$, and the animals were then endotracheally intubated in

the prone position. The animals' eyes were closed and their ears plugged. Surgery was performed in the supine position, and experiments made in the left lateral position. General anesthesia was maintained with 6.6% of desflurane in 40% oxygen, corresponding to 0.5 minimal alveolar concentration (MAC) in the present experimental model (unpublished observations), together with continuous i.v. infusions of fentanyl $0.040\,mg\,kg^{-1}\cdot h^{-1}$ and vecuronuim $2.0\,mg\,kg^{-1}\cdot h^{-1}$ during surgical preparation, and with continuous infusions of ketamine $15\,mg\,kg^{-1}\cdot h^{-1}$ and vecuronium $2.0\,mg\,kg^{-1}.h^{-1}$ during the experimental period (Fig. 1).

Ventilation

Ventilation was accomplished with a volume-controlled ventilator (Servo-Ventilator 900, Siemens-Elema, Solna, Sweden) delivering tidal volumes of $14\text{–}16\,ml\,kg^{-1}$ at a respiratory rate of $12\text{–}18\,min^{-1}$. Inspired and expired concentrations of carbon dioxide, oxygen and desflurane were monitored with an Ohmeda 5250 RGM gas analyzer (Ohmeda, Swindon, UK).

Miscellaneous

All intravascular catheters were inserted by surgical cutdown under clean though nonsterile conditions. Electrocautery was used to minimize blood loss.

The animals were kept normothermic (38.0°C).

A balanced 2.5% glucose solution (Rehydrex®, Pharmacia, Sweden) was infused at a rate of $3\text{–}4\,ml\,kg^{-1}\cdot h^{-1}$, and urine output was measured via a suprapubic (cystostomy) catheter.

Cerebral hemodynamics

Surgical preparation has been reported in detail elsewhere (8). The right common carotid artery was cannulated with a 45-mm 20-G catheter for injection of the ^{133}Xe tracer substance (Mallinckrodt, UK). The two main branches, the occipital and external carotid arteries, were both identified and ligated 5 mm distal to their bifurcations (9).
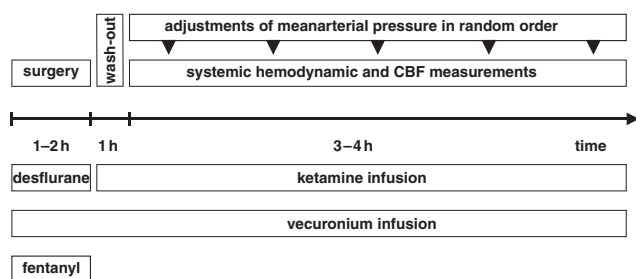

Fig. 1. Schematic presentation of experimental design.

Cerebral blood flow (CBF) measurements based on a modification of the Kety-Schmidt method were carried out with ^{133}Xe as a tracer. The tracer substance was injected into the internal carotid artery and the cerebral clearance curve recorded with an extracranial sodium-iodide scintillation detector over the ipsilateral parietotemporal region. Between 0.5 and 1 MBq of isotope dissolved in saline was used for each measurement. A Novo Cerebrograph 10a CBF device (B Simonsen Medical AS, Randers, Denmark) was used to record the detector counts and calculate mean cortical hemispheric CBF by mono-exponential approximation of the initial segment of the clearance curve corrected for background activity. Two series of measurements were made at each MAP level and their mean values were used in further analyses.

Static autoregulatory response was calculated as the percentile change in CBF per mmHg change in MAP. Estimated cerebral vascular resistance (CVRe; kPa $.100\,g\,min\,ml^{-1}$) was calculated from corresponding MAP and CBF values as CVRe=MAP/CBF, assuming the intracranial pressure to be zero.

Systemic hemodynamics

Both femoral arteries were cannulated. A 20-G 45 mm Teflon catheter (Intraflow, Viggo AB, Helsingborg, Sweden) was inserted and used for invasive pressure measurements and arterial blood sampling. In the opposite femoral artery a COOK 8.5F balloon dilation catheter (William Cook Europe, Bjaeverskov, Denmark), model Omega NV™ (inflated balloon size 25×80 mm), was introduced and positioned with its tip in the mid-portion of the descending aorta close to the heart and 2–4 cm below the diaphragm (Fig. 2). A 7.0F Meditech PTA balloon catheter (Boston Scientific, Galway, Ireland), model XXL/14–4/5,8/75, was introduced in the femoral vein and positioned with its tip in the inferior caval vein 2–4 cm below the diaphragm (Fig. 2).

In the external jugular vein a 5F Swan-Ganz catheter (Ohmeda, Swindon, UK) was inserted and positioned to measure central venous pressure (CVP), and core temperature, and also to measure cardiac output (CO) following rapid 10-ml injections of room tempered 5% glucose solution. Systemic vascular resistance (SVR; $dynes \cdot s \cdot cm^{-5}$) was calculated as MAP–CVP/CO·79.9. Heparin $250\,IU\,kg^{-1}$ i.v. was given as soon as the catheters had been inserted, and their correct positions were verified at autopsy.

Drug concentrations

Throughout the experiment, i.v. infusions of fluid and anesthetic drugs were given in a hind leg, and blood was sampled from a femoral artery.
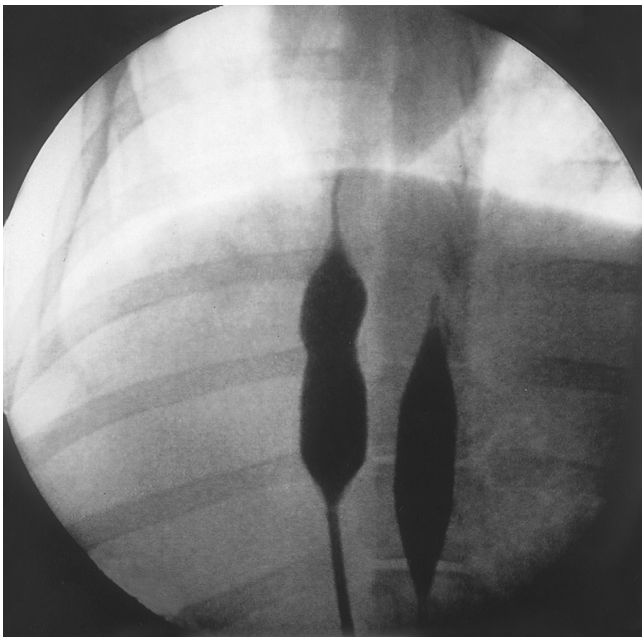
Fig. 2. Radiographic picture of intravascular inferior caval (left) and aortic (right) balloons positioned in the lower thoracic region close to the heart. The balloons were used to reduce or raise systemic arterial blood pressure in the upper body region by decreasing cardiac preload or increasing cardiac afterload, respectively.

Blood samples for ketamine and norketamine analysis were drawn before each filling and each release of the aortic or caval balloons used to adjust the MAP at predetermined levels.

Ketamine and norketamine were assayed in hemolyzed blood by gas liquid chromatography (GLC) (10). Fentanyl in plasma was determined by GLC with N2-selective detection using an OV-17-packed column instead of a capillary column (11).

Experimental design

The experimental period, following a 60-min period of stabilization after the desflurane and fentanyl had been exchanged for ketamine, lasted between 180 and 240 min. For assessments of cerebrovascular autoregulation at different cerebral perfusion pressures, the aortic balloon was filled with saline to increase cardiac afterload and raise MAP, or the caval balloon was filled accordingly to decrease cardiac preload and reduce MAP. Balloon volumes were adjusted to attain predetermined levels of MAP within the expected normal range of cerebrovascular autoregulation in the pig, aiming at MAP levels differing by -40%, -20%, $+20\%$ or $+40\%$ from the baseline level determined at steady-state ketamine anesthesia. Balloon adjustments were made in a random order. Values of

CBF and systemic hemodynamic variables were obtained at each MAP level. Ventilation was adjusted as required, by altering respiratory rate, to maintain endtidal normocapnia in each animal.

Individual regression and correlation coefficients of linear pressure-flow response curves were calculated from five values of MAP and CBF, respectively, obtained from each animal.

Immediately after the experimental period the CBF was measured once more to enable assessment of physiological stability over time.

On completion of each experiment the animal was sacrificed by an i.v. overdose of pentobarbital, and adequate positions of all catheters were verified at autopsy.

Statistical considerations

Mean values of the two CBF measurements at each MAP level were used. Percentages were calculated from the mean values but values in text and tables are given as median with 25th and 75th percentiles in parenthesis when not stated otherwise.

Student's *t*-test was used for analysis of parametric data and the Mann–Whitney *U*-test was used for analysis of nonparametric data. Multiple regression analysis was used to compare individual data on cerebrovascular autoregulation.

A *P*-value of 0.05 or less was considered as statistically significant. Statistical calculations were made using the Statistica$^{\text{TM}}$ software package (StatSoft Ltd, Tulsa, OK)

Results

Cerebrovascular autoregulation

In eight animals with a baseline CBF of 53 (42, 57) ml $.100\,g^{-1}.min^{-1}$, a mean reduction of MAP by 40% and a mean increase in MAP by 43% induced a mean reduction of CBF by 15% and a mean increase in CBF by 12%, respectively. Correspondingly, the CVRe decreased by 31% and increased by 31%, respectively (Table 1 and Fig. 3). Static autoregulatory response for all eight animals was 0.33 ± 0.086 (mean $\pm$SEM).

The mean regression coefficient of all animals was 0.18 with a 95% confidence interval of -0.02 to 0.34. This interval does not include 0.64, i.e. the regression coefficient of a linear curve through origo, indicating complete lack of cerebrovascular autoregulation and determined with a determination coefficient exceeding 0.99 in the eighth animal. This animal had a completely pressure-dependent flow pattern and was

Table 1

Cerebral and systemic hemodynamic variables.

| | Intended change in mean arterial blood pressure | | | | |
	−40%	−20%	Baseline	+20%	+40%
Change in mean arterial pressure (%)	−39.8	−19.7	0	+26.2	+43.1
Mean arterial pressure (mmHg)	60 (58;62) 59* (57;62)	82 (81;85) 83* (80;86)	102 (96;109) 101* (94;109)	129 (122;134) 128* (119;132)	140 (138;156) 140* (136;152)
Cerebral blood flow (ml.100 g^{-1}.min^{-1})	41.0 (35.0;47.6) 38.6* (34.3;47.9)	42.2 (38.9;49.3) 41.2* (38.7;50.0)	52.6 (42.4;57.0) 53.8* (40.8;57.4)	52.9 (47.9;57.0) 50.5* (46.8;55.4)	50.4 (46.2;59.0) 49.4* (45.1;55.9)
Estimated cerebral vascular resistance (mmHg.100 g.min.ml^{-1})	1.6 (1.2;1.8) 1.4* (1.2;1.7)	1.9 (1.5;2.2) 2.1* (1.6;2.2)	2.0 (1.7;2.5) 2.3* (1.7;2.6)	2.2 (2.1;2.6) 2.3* (2.3;2.8)	2.4 (2.4;3.0) 2.8* (2.4;3.4)
Arterial 02 tension (kPa)	21.6 (19.3;23.4)	22.3 (16.5;26.9)	23.4 (21.4;26.9)	26.1 (23.8;26.6)	27.3 (24.2;28.7)
Arterial C02 tension (kPa)	4.9 (4.7;5.4)	5.1 (4.9;5.3)	5.0 (4.7;5.2)	4.7 (4.5;5.0)	4.7 (4.2;5.1)
Arterial pH	7.38 (7.36;7.41)	7.42 (7.41;7.43)	7.44 (7.42;7.46)	7.46 (7.43;7.48)	7.45 (7.40;7.46)
Arterial base excess (mmol.l^{-1})	−2.6 (−4.6;0.1)	0.6 (−0.2;1.5)	2.2 (0.3;3.3)	1.1 (−0.3;2.3)	−1.1 (−2.0;0.3)
Heart rate (min^{-1})	171 (150;197)	157 (145;196)	149 (142;161)	139 (115;158)	129 (122;153)
Cardiac output (l.min^{-1})	1.7 (1.3;2.0)	1.9 (1.4;2.8)	2.4 (2.0;3.1)	2.8 (2.4;3.2)	3.4 (2.6;4.0)

Hemodynamic and arterial blood gas data [median (25th, 75th percentiles)] in all eight animals and * excluding the eighth nonautoregulating animal.

found to respond with mean CBF levels ranging between 34 and 96 ml .100 $g^{-1}min^{-1}$ when MAP had been titrated at 59–155 mmHg (Fig. 3).

Systemic hemodynamics

Data on the systemic hemodynamic effects of ketamine infusion at the five various MAP levels are presented in Table 1. During use of the caval balloon to reduce MAP by 40%, mean heart rate increased by 16%, mean CO decreased by 35%, and mean arterial Base Excess (BE) decreased from 1.7 to 2.1, whereas arterial pH and SVR remained unchanged.

When used to raise MAP by 43%, the aortic balloon was found to decrease mean heart rate by 13%,

Fig. 3. Cerebral blood flow (CBF) values at different mean arterial pressure (MAP) levels for all eight animals studied. The dotted line represents the pressure-dependent CBF values found in the eighth animal.

increase mean CO by 35%, and to decrease mean BE from 1.7 to 1.0, whereas no changes were found in arterial pH and SVR.

Other physiological variables

During the experiment the mean core temperature was maintained at 38.0 (37.6, 38.7)°C.

Drug concentrations

Mean plasma concentrations of fentanyl were 11.1 (9.1, 12.7) ng ml^{-1} during continuous infusion of fentanyl at 0.040 mg $kg^{-1}h^{-1}$ and 2.7 (2.5, 3.3) ng ml^{-1} 60 min after the infusion had been stopped.

During the 15 mg $kg^{-1}·h^{-1}$ infusion of ketamine the mean blood concentration of ketamine was 5.9 (4.6, 7.4) µg ml^{-1}. Concentrations of ketamine in blood obtained from the femoral artery were 6.3 (3.5, 6.9) µg ml^{-1} before occlusion of the caval balloon to produce a 40% mean decrease in MAP and 7.4 (3.5, 9.4) µg ml^{-1} immediately before release, and 4.5 (4.3, 5.6) µg ml^{-1} before occlusion of the aortic balloon for a 43% increase in MAP and 6.4 (4.2, 6.8) µg ml^{-1} just before release. There were no statistically significant differences in the ketamine concentration between the blood samples obtained from the femoral artery immediately before inflation and immediately after deflation of the aortic or caval balloons ($P=0.12$ and $P=0.47$, respectively).

The concentration of norketamine increased slowly during the infusion to reach a maximum of 5.0 (4.3, 5.7) µg ml^{-1} after 4.1±0.55 h of infusion.
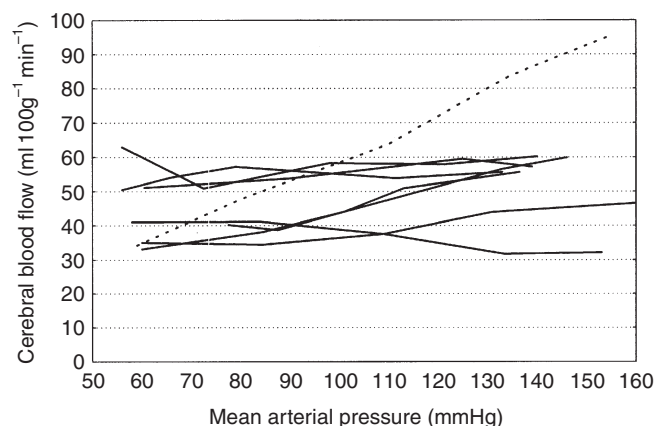
Discussion

Effects on cerebrovascular autoregulation

To our knowledge this is the first study addressing the effects of racemic ketamine on autoregulation of cerebral blood flow, and our main finding that ketamine does not abolish cerebrovascular autoregulation is consistent with two recent reports regarding the enantiomer S (+)-ketamine in a rat model (12) and in patients (13).

Ketamine has been reported to increase (1–5) but also to decrease (6, 7) CBF. These divergent results between different studies have been suggested to result from ketamine-induced abolishment of cerebrovascular autoregulation, resulting in pressure-dependent passive changes in CBF (14, 15), and various dose- or time-dependent cerebrovascular effects of ketamine and of other vasoactive anesthetic drugs including vasopressors or vasodilators given simultaneously to maintain physiological stability (16, 17). Differences in the species studied, in arterial CO_2 tension level and stability, as well as in technique for CBF determination make these findings even more difficult to interpret and compare. Some of these results could be explained by an impaired or abolished cerebral autoregulation (14, 15).

One of our animals had a nonautoregulating pattern with passive pressure-dependent CBF at MAP values ranging between 59 and 155 mmHg, and on extrapolation this MAP/CBF graph was found to approximately hit the zero-point of the CBF and MAP axes. In addition the direct MAP/CBF linearity with correlation and determination coefficients, both exceeding 0.99, indicates considerable influence of the independent variable (MAP) on the dependent one (CBF), i.e. virtually passive pressure-dependent flow characteristics, in this experiment. An explanation for this aberrant result could neither be found during that experiment nor at postmortem autopsy, but as autoregulatory patterns, although slightly impaired in two animals, were found in the seven other animals, we conclude that this experimental model enables repeated valid assessments of cerebrovascular autoregulation. Even including this nonautoregulating animal the values of mean static autoregulatory response was well below the proposed thresholds of impaired autoregulation of 0.5 and 1.5% changes in CBF per mmHg change in MAP previously reported to indicate impaired cerebrovascular autoregulation in humans (18, 19).

Blood pressure limits of cerebrovascular autoregulation during ketamine anesthesia were never determined in this study.

Effects of confounding factors

The choice of background anesthesia seems to play a crucial role when studying the effects of an anesthetic drug, e.g. ketamine, on CBF. Ketamine has been reported to increase CBF in awake or lightly anesthetized animals and humans (3, 4), whereas no changes in CBF (20) or CBF velocity (21, 22) were found on ketamine injection when, instead, cerebral depressant anesthetic drugs were used for background anesthesia.

In several early studies and reports, an increase in CBF reported to be associated with the administration of ketamine was probably related to drug-induced hypoventilation resulting in hypercarbia-induced cerebral vasodilatation rather than to direct cerebrovascular effects of ketamine (1, 2, 4). In contrast, no increases in CBF have been found in corresponding studies (1, 23), where ventilation was controlled throughout the experiments. These findings emphasize the importance of maintaining stability of $PaCO_2$ over time in experimental studies on ketamine, i.e. using mechanical ventilation adjusted according to continuous endtidal CO_2 monitoring and frequent arterial blood gas analyses.

Being able to manipulate the mean blood pressure level is crucial in studies on the autoregulation of an organ. To our knowledge, vasoactive drugs (24–27), controlled hemorrhage (12) or venous balloon catheters (24–27) have been used to increase or decrease MAP levels in all available experimental models designed for this purpose except one (28), where xenon was studied with a model similar to ours and including both venous and arterial balloon catheters. By entering the target organ to be studied, e.g. by crossing the blood–brain barrier, vasoactive drugs may directly influence regional tissue perfusion, i.e. in this case that of the brain, with potentially confounding results. Such pharmacodynamic interactions should be minimized or preferably avoided in an experiment designed to study the influence of a certain drug on cerebrovascular autoregulation.

Another concern regarding this model was that inflation of the aortic balloon might induce tissue hypoxia in the lower body region with metabolic acidosis, but apparently the periods of partial aortic occlusion were neither long nor extensive enough to induce metabolic acidosis of any significance in any animal.

Our method of CBF determination following intra-arterial injection of ^{133}Xe with extracranial scintillation detection has been validated earlier in this species and allows for frequently repeated measurements (8). By further reducing the amount of isotope injected on each measurement we were able to decrease the

interval between measurements and thereby enhance the resolution in time for the pharmacodynamic response.

The ketamine infusion rate chosen in this study, 15 mg kg^{-1}·h^{-1}, corresponds to anesthetic blood concentrations of at least $4 \mu g \, ml^{-1}$ in this species (23). In rats, the enantiomer S (+)-ketamine has been shown to have different effects on the autoregulatory curve at infusion rates of 30 and 60 mg kg^{-1}·h^{-1}, respectively (12), which could be explained, at least in part, by a different sympathetic influence on cerebrovascular tension at different levels of anesthesia. Such dose-dependent effects of racemic ketamine on autoregulation of CBF cannot be elucidated by our results, as only one ketamine infusion rate was used.

Although one animal displayed a nonautoregulating pattern, we conclude that cerebrovascular autoregulation is not abolished during ketamine anesthesia, because for the remaining animals the CBF during continuous infusion of ketamine was found to be maintained at a level significantly different from pressure passive flow at different MAP achieved without the use of vasoactive drugs. These findings also indicate that previous divergent conclusions regarding the cerebral hemodynamic effects of racemic ketamine are unlikely to result from severe impairment of cerebrovascular autoregulation caused by the ketamine.

Acknowledgements

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