Laboratory Investigation

Movement associated with high cerebral concentrations of isoflurane: no evidence of seizure activity

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Purpose: This study examined the effect of high cerebral concentrations of isoflurane on the electroencephalogram (EEG) and motor activity while using an experimental preparation in which isoflurane can be selectively delivered to the in situ goat brain. In a previous study we found that isoflurane (>6%), when selectively delivered to the brain, was associated with spontaneous movement.

Methods: In each of six goats, the cerebral circulation was isolated and cannulae inserted into a carotid artery and the jugular veins to permit selective delivery of isoflurane using a bubble oxygenator-roller pump system. The EEG was measured while isoflurane (1.3%, 3% and 10–12%) was delivered to the brain; isoflurane concentration in the torso during these periods was 1.3%, 0.3% and 0.3% respectively.

Results: The EEG was active at isoflurane 1.3% but was isoelectric with spike activity at 3% and 10–12%; EEG power decreased from $32,249 \pm 15,241 \mu V^2$ (mean $\pm$ sd) during the control period (isoflurane = 1.3%) to $1761 \pm 2435 \mu V^2$ when

cranial isoflurane = 3%, and $3346 \pm 4780 \mu V^2$ when cranial isoflurane = 10–12% ($P < 0.05$). When cranial isoflurane concentration was 10–12%, with the torso isoflurane concentration at 0.3%, spontaneous motor activity occurred, including stiffening, extremity and jaw movement and blinking. The EEG returned to normal when isoflurane concentration was decreased to 1.3%.

Conclusion: The presence of spontaneous movement with concomitant high cranial concentrations of isoflurane and isoelectric EEG is unexplained, but is consistent with a facilitatory effect of isoflurane on motor activity, presumably at a subcortical level.

Objectif: Ce travail étudie l'effet d'une haute concentration d'isoflurane sur l'électroencéphalogramme (EEG) et l'activité motrice à l'aide d'une préparation expérimentale qui permet de livrer l'isoflurane sélectivement au cerveau de la chèvre. Au cours d'une étude antérieure, les auteurs ont découvert que l'apport sélectif d'isoflurane (>6%) au cerveau provoquait des mouvements spontanés.

Méthode: La circulation cérébrale de six chèvres a été isolée et des canules insérées dans une carotide et les veines jugulaires pour permettre la livraison de l'isoflurane avec un système d'oxygénéateur à bulle/pompe à galet. L'EEG a été enregistré sous des concentrations d'isoflurane (1,3%, 3% et 10–12%) livrées au cerveau; au niveau du thorax, les concentrations correspondantes ont été respectivement de 1,3%, 0,3% et 0,3%.

Résultat: L'EEG était actif à la concentration de 1,3% mais isoelectrique avec une activité de pointes à 3% et à 10–12%; le voltage de l'EEG a diminué pendant la période contrôle (isoflurane 1,3%) de $32\,249 \pm 15\,241 \mu V^2$ (moyenne $\pm$ ET) à $1\,761 \pm 2\,435 \mu V^2$ lorsque l'isoflurane intracrânien était à 3% et à $3\,346 \pm 4\,780 \mu V^2$ avec l'isoflurane intracrânien à 10–12% ($P < 0,05$). Quand la concentration intracrânienne

Key words

ANAESTHESIA: mechanisms;
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d'isoflurane était à 10–12%, avec une concentration thoracique à 0,03%, une activité motrice spontanée est apparue, sous la forme de raideur, mouvements des extrémités et de la mâchoire, et clignotement des yeux. L'EEG est revenu à la normale quand la concentration d'isoflurane a été ramenée à 1,3%.

Conclusion: *L'apparition de mouvements spontanés et d'une isoélectricité EEG simultanément à une haute concentration d'isoflurane demeure inexpliquée, mais semble compatible avec un effet facilitatoire présumé sous-cortical de l'isoflurane sur l'activité motrice.*

As an animal (or human) is anaesthetized, it enters various stages, including an excitement phase, surgical anaesthesia and deep anaesthesia;¹ this latter stage results in profound brain depression. At these high anaesthetic concentration (or above) spontaneous motor activity should not occur. In a recent study we examined cardiovascular responses to a noxious stimulus utilizing an experimental preparation which permits selective delivery of high concentrations of isoflurane to the *in situ* goat brain. We noted spontaneous movement when cerebral isoflurane concentration was greater than $\approx 6\%$.² These animals either had spontaneous, purposeful movement or stiffened, consistent with seizure activity. Because isoflurane is an isomer of enflurane and the latter can cause seizure activity,³ we hypothesized that isoflurane at very high concentrations could, likewise, cause seizures. The purpose of the present study was to examine the effects of high concentrations of isoflurane in the brain and to detect electroencephalographic evidence of seizure activity when these movements occurred.

Methods

This study was approved by the animal care committee. Adult female dairy goats ($n = 6$) weighing 43 ± 9 kg were anaesthetized with isoflurane 5% via mask. The trachea of each animal was intubated and the lungs mechanically ventilated. A 16-gauge intravenous catheter was inserted into a peripheral vein. End-tidal gases were measured with a calibrated Puritan-Bennett anaesthetic agent analyzer (Datex, Inc., Tewksbury, MA). A rumen tube was placed into the stomach to drain rumen contents. Bilateral neck dissections were performed to isolate the external jugular veins and the carotid arteries as previously described.^{4–6} The occipital arteries were also dissected free and ligated. A catheter was placed into a carotid artery to measure systemic mean arterial pressure (MAP) and to obtain blood for arterial gas analysis, haematocrit and glucose. The animal was given heparin, $400 \text{ U} \cdot \text{kg}^{-1}$, and the carotid artery was

cannulated with a large catheter for preparation for cerebral bypass. An external jugular vein was cannulated with a Y-cannula which permitted cranial venous blood to drain either into the torso or to be diverted to a bubble oxygenator/roller pump system.^{4–6} A single cannula was placed in the other external jugular vein to drain additional blood to the bypass unit as needed. To measure cranial blood pressure during bypass, an 18-gauge catheter was placed into the remaining carotid artery and directed toward the head; and adjustable ligature placed around this carotid artery, when tightened, prevented blood flow from the torso to the head during bypass. Body temperature was measured with a rectal probe and maintained at $36.3 \pm 0.7^\circ\text{C}$ with a heating lamp. Cranial temperature was measured with a nasopharyngeal probe and maintained at $36.4 \pm 0.7^\circ\text{C}$. During bypass, a water bath for the oxygenator unit was used to adjust cranial temperature.

Steel screws were placed into the skull to monitor the electroencephalogram (EEG). Each hemisphere was monitored with frontal-occipital leads. The EEG was recorded with a LifeScan EEG monitor (Neurometrics, Inc., San Diego, CA) which recorded the power (amplitude squared) in the alpha (8–12 Hz), beta (13–30 Hz), delta (0–3 Hz) and theta (4–7 Hz) bands using five one-minute epochs. Electrode impedance was < 7000 ohms.

Each animal was maintained at isoflurane $\approx 1.4\%$ (1 MAC in the goat⁴) for at least 20 min and control EG data were collected for five minutes. Lactated Ringer's solution (2–3 L) was administered and blood (≈ 500 ml) was drained from the goat to prime the bubble oxygenator (Bentley B5, Baxter, Inc., Irvine, CA). Gas flow ($95\% \text{ O}_2/5\% \text{ CO}_2$) to the oxygenator was $3 \text{ L} \cdot \text{min}^{-1}$. An enflurane vaporizer filled with isoflurane was placed in line with the gas flow. This permitted delivery isoflurane in high (10–12%) concentrations to the bubble oxygenator. A catheter was passed through the exhaust tubing into the centre of the oxygenator. A calibrated Puritan-Bennett agent analyzer sampled the exhaust gas in an air-tight manner. The isoflurane concentration measured from the exhaust of the bubble oxygenator is a reasonable estimate of the isoflurane concentration (partial pressure) in the arterial blood of the oxygenator.^{4–6} Although the agent analyzer is calibrated only to 5%, calculations based upon misfilling an enflurane vaporizer with isoflurane⁷ suggest that the analyzer was accurate to $\pm 10\%$ of the measured values above 5%.

Bypass was initiated by diverting cranial venous blood to the oxygenator and infusing arterialized blood into the head via the carotid artery. The temporary ligature around the other carotid artery prevented systemic arterial blood from entering the head. Glucose ($10\text{--}20 \text{ mg} \cdot \text{min}^{-1}$) was infused into the oxygenator. Bypass

TABLE I Electroencephalographic data

	<i>Pre-bypass</i>	<i>Bypass-1.3%</i>	<i>Bypass-3%</i>	<i>Bypass-10%</i>	<i>Post-bypass</i>
Power (μV^2)	32,249 $\pm$ 15,241	22,695 $\pm$ 7431	1761 $\pm$ 2435*	3346 $\pm$ 4780*	22,859 $\pm$ 4902

Mean $\pm$ standard deviation.

* $P < 0.05$ compared with Pre-bypass, Bypass-1.3% and Post-bypass values.

EEG = electroencephalogram; Pre-bypass = values obtained prior to bypass with isoflurane = 1.4%; Bypass-1.3% = value obtained during bypass with torso and head at 1.3% isoflurane. Bypass-3% = value obtained during bypass with torso isoflurane concentration at 0.3% and cranial isoflurane concentration at 3%. Bypass-10% = value obtained during bypass with torso isoflurane concentration at 0.3% and cranial isoflurane concentration at 10%. Post-bypass = value obtained after bypass with isoflurane concentration in torso and head at 1.3%. The EEG was isoelectric with spike activity when isoflurane concentration in the head was 3% or greater.

TABLE II Blood gases, haematocrit and glucose

	<i>pH</i>	<i>PCO₂</i> (mmHg)	<i>PO₂</i> (mmHg)	<i>BE</i> (mM)	<i>Hct</i> (%)	<i>Glucose</i> (mg $\cdot$ dl ⁻¹)
Pre-bypass	7.34 $\pm$ 0.04	44 $\pm$ 4	404 $\pm$ 141	-2 $\pm$ 4	29 $\pm$ 4	56 $\pm$ 14
Bypass						
- Torso	7.30 $\pm$ 0.04	44 $\pm$ 8	302 $\pm$ 177	-5 $\pm$ 1	21 $\pm$ 1	65 $\pm$ 18
- Arterial	7.31 $\pm$ 0.02	40 $\pm$ 1	545 $\pm$ 25	-6 $\pm$ 2	22 $\pm$ 3	73 $\pm$ 25
- Venous	7.27 $\pm$ 0.03	47 $\pm$ 2	235 $\pm$ 119	-6 $\pm$ 2	22 $\pm$ 4	70 $\pm$ 23
Post-bypass	7.37 $\pm$ 0.06	36 $\pm$ 5	347 $\pm$ 126	-3 $\pm$ 3	23 $\pm$ 3	73 $\pm$ 27

BE = Base excess; Hct = haematocrit; Pre-bypass = value obtained prior to bypass; Torso = value obtained from systemic circulation during bypass; Arterial = value obtained from arterial limb of bypass circuit; Venous = value obtained from venous limb of bypass circuit; Post-bypass = value obtained after bypass.

flows, maximized depending upon venous return, were approximately 10–25 ml $\cdot$ kg⁻¹ $\cdot$ min⁻¹; isoflurane was kept at 1.3% in the torso and head. The EEG activity was again recorded for five minutes. The torso isoflurane concentration was decreased to 0.2–0.4% and the cranial isoflurane increased to $\approx$ 3%, which represents the approximate balance needed to achieve 1 MAC of anaesthesia in this surgical preparation.⁴ Following EEG measurement of this stage, cranial isoflurane was increased to 10–12% and the EEG continually recorded. We looked for spontaneous movements. Once the cranial isoflurane concentration was 10–12% and had stabilized for 10–15 min, the bypass was discontinued and the native circulation re-established. After 15 min of stabilization, the EEG was again recorded.

Data are expressed as mean $\pm$ standard deviation. EEG power was analyzed with repeated measures analysis of variance with $P < 0.05$ considered significant.

Results

During the control period, the EEG was active at isoflurane 1.4%, with power distributed predominantly in the delta and theta bands, with some activity in the alpha and beta bands. During bypass with cranial and torso isoflurane concentrations at 1.3%, there was no change in the EEG (Table I). When the torso isoflurane concen-

tration was 0.3% and cranial isoflurane concentration was 3%, the EEG was isoelectric, with spike activity. There was no spontaneous movement although some animals continued to shiver as they had during the control period. When cranial isoflurane concentration was increased to 10–12%, five of six animals had spontaneous movement, including stiffening, jaw motion, blinking and extremity movement. The EEG was still isoelectric with spike activity. Post-bypass, EEG activity returned (Table I). The Figure shows the raw EEG in an animal during the control, bypass and post-bypass periods. In one animal progressive hypoxaemia caused EEG suppression and prevented meaningful EEG data collection at 10% isoflurane and post-bypass. Because of difficulty with arterial inflow in another animal, we did not study it with 1.3% isoflurane in torso and head; this was one of the animals that moved.

Systemic MAP was 113 $\pm$ 29 mmHg pre-bypass, 83 $\pm$ 23 mmHg during bypass when torso and head isoflurane concentrations were 1.3%, 104 $\pm$ 25 mmHg when cranial isoflurane concentration was 3%, 122 $\pm$ 45 mmHg when cranial isoflurane concentration was 10–12% and 87 $\pm$ 13 mmHg post-bypass. The corresponding cranial MAPs were 86 $\pm$ 36 mmHg, 46 $\pm$ 5 mmHg, 39 $\pm$ 7 mmHg, 36 $\pm$ 5 mmHg and 65 $\pm$ 17 mmHg, respectively.

During bypass and post-bypass, haematocrit de-

FIGURE Electroencephalogram (EEG) of an animal. (A) Pre-bypass, isoflurane = 1.3%. (B) Bypass, cranial and torso isoflurane = 1.2%. The EEG is active. (C) Bypass, cranial isoflurane = 3.2%, torso isoflurane = 0.4%. The EEG is isoelectric, with spike activity. (D) Bypass, cranial isoflurane = 10%, torso isoflurane = 0.4%. The EEG is isoelectric, with spike activity. (E) Post-bypass, isoflurane = 1.3%. The EEG is active.

creased slightly and base excess increased slightly. Glucose was maintained in the normal range throughout the study (Table II).

Discussion

Five of six animals had movement of unknown aetiology when the isoflurane concentration in the head was 10–12% and 0.3% in the torso. In our previous study, we initially speculated that this movement represented seizure activity.² Isoflurane has rarely been associated with seizure activity.⁸ In the present study we found that at high isoflurane concentrations the EEG was isoelectric with spike activity. However, there was no overt seizure activity. In a previous study, we found that when isoflurane concentration was 0.2–0.3% in the torso, isoflurane 3% was required in the brain to suppress movement in response to a noxious stimulus.⁴ This suppression may have been due to increased descending inhibition. Shimoji *et al.* found that halothane 2% (compared with halothane 1–1.5%) increased inhibitory responses of neurons in the midbrain reticular formation.⁹ Extrapolating these data to our previous study and the present one, it is possible that there was a balance of inhibitory and excitatory influences on the spinal cord when cranial isoflurane was 3%, in part due to descending inhibition. When cranial isoflurane concentration was increased to 10–12%, subcortical structures responsible for this descending inhibition (i.e., midbrain reticular neurons) could have been suppressed, which permitted spinal excitatory neurons to be unopposed. This explanation is speculative, however, future studies using electrophysiological monitoring of critical areas (e.g., midbrain reticular neurons) might aid in the elucidation of the mechanism.

It is possible that the blood pressure difference between the torso and head permitted isoflurane-poor blood to flow into the cerebral system (via small collaterals) thereby decreasing the isoflurane concentration in the head. This is not likely, particularly at the cortical level, since the EEG remained isoelectric. We previously demonstrated that this experimental preparation isolates the cerebral circulation at the level of the caudal medulla or upper cervical cord.⁵ However, the pressure difference between the torso and head was greater in the present investigation than in our previous study⁵ so that it is possible that isoflurane-poor blood washed out the isoflurane in subcortical structures. This does not seem probable because the blood pressure difference at 10–12% cranial isoflurane was nearly the same as the blood pressure difference when cranial isoflurane was 3%, and movement occurred in the former and not the latter.

These high concentrations of isoflurane in the brain can depress cardiovascular responses to noxious stimuli applied to an extremity.² It is interesting to note that we found serendipitously that in two animals MAP increased when the lip was stimulated but not when an

extremity was stimulated despite the fact that cranial isoflurane was 10–12% (data not reported). One would expect that the high cranial isoflurane would result in a functional state similar to brain death, and extremity stimulation should increase MAP, similar to what occurs when a noxious stimulus (skin incision) is applied to a brain dead human undergoing organ harvest.¹⁰ We have found in a previous study that the anaesthetic effects of isoflurane in the periphery are not important at least as regards movement.¹¹ Whether or not anaesthetic effects on peripheral nociceptors are important *vis-à-vis* cardiovascular changes is unclear as we did not document the changes in blood pressure or heart rate that occurred during the stimulation of the periphery.¹¹

In summary we have documented spontaneous motor activity associated with high cerebral concentrations of isoflurane. Our original hypothesis that it represented seizure activity appears incorrect. The cause of this movement remains unknown.

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