Effect of sevoflurane on spontaneous sympathetic activity and baroreflexes in rabbits

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Summary
Sevoflurane causes a decrease in mean arterial pressure (MAP). We have studied in anaesthetized rabbits its interactive effects on MAP, the autonomic nervous system and baroreflexes. During sevoflurane administration changes in renal sympathetic nerve activity (RSNA) and heart rate (HR) were observed: (1) when the normal decrease in MAP occurred; (2) when this was prevented by angiotensin II; (3) during a similar decrease in MAP induced by infusion of sodium nitroprusside (SNP) without sevoflurane administration; and (4) during pressor and depressor responses to phenylephrine and SNP. There was a reduction in MAP from 80 to 40 mm Hg after 1–4% sevoflurane without changes in HR, while RSNA remained unchanged only up to concentrations of 3% and was depressed by 37% (P < 0.05) with 4% sevoflurane. When MAP was maintained constant with angiotensin II, both HR and RSNA decreased, by 12% and 69%, respectively, after 4% sevoflurane (P < 0.05). A decrease in MAP of 40 mm Hg during infusion of SNP increased HR and RSNA by 22% (P < 0.05) and 150% (P < 0.01), respectively. At 2% sevoflurane, baroreflex sensitivity (i.e. ΔRSNA/ΔMAP and ΔHR/ΔMAP) was depressed by 36% and 57%, respectively, for the pressor effects of phenylephrine, and by 89% and 81%, respectively, for the depressor effects of SNP. We conclude that the baroreflexes continued to compensate for the effects of sevoflurane on sympathetic and cardiomotor activity with concentrations up to 3% and 4%, respectively. (Br. J. Anaesth. 1998; 80: 68–72)

Keywords: anaesthetics volatile, sevoflurane; sympathetic nervous system; reflexes, baroreceptor; rabbit

Sevoflurane causes a concentration-related haemodynamic depression, particularly of mean arterial pressure (MAP) which normally activates baroreflexes to cause an increase in heart rate (HR) and sympathetic activity. Alternatively, sevoflurane could cause a decrease in HR and sympathetic activity as a result of its central effects. However, the peripheral, central and baroreflex effects of sevoflurane interact, but hitherto there has been little work on their relative contributions to its perceived effects on the circulation. For example, Saeki and colleagues showed that up to 1.25 MAC of sevoflurane did not produce significant changes in renal sympathetic nerve activity (RSNA) in rabbits. In humans, sevoflurane, at concentrations of 0.4–1.2 MAC, did not affect sympathetic nerve activity supplying skeletal muscle. Thus the limited data available could suggest that although sevoflurane depresses baroreflexes, they continue to respond to some extent to a reduction in MAP, thereby maintaining the observed stability of RSNA and HR.

In this study we have tested the hypothesis that baroreflexes, although depressed, maintain a response to a reduction in MAP sufficient to mitigate the depressant effects of clinically used concentrations of sevoflurane on the autonomic nervous system.

Materials and methods
GENERAL PROCEDURES

The study was approved by the UK Home Office (license PPL 90/00852). We studied 22 New Zealand White rabbits of both sexes, weighing 3.5–4.0 kg. Anaesthesia was induced with methohexital 10–15 mg kg⁻¹ i.v. and maintained with 1% α-chloralose in an initial bolus dose of 30 mg kg⁻¹ i.v., followed by a continuous infusion of 15–20 mg kg⁻¹ h⁻¹. A tracheotomy was performed and the lungs were ventilated artificially (SLE 2000, SLE Ltd, UK) with oxygen-enriched air. Neuromuscular block was maintained using bolus doses of succinylcholine 2 mg kg⁻¹ i.v. every 20–30 min. A femoral artery and vein were cannulated for recording arterial pressure, sampling of blood and infusion of 1% α-chloralose. The right and left marginal ear veins were cannulated, one for infusion of fluids and the other for administration of test drugs. Oesophageal temperature was measured with a thermistor (Yellow Springs Instruments, OH, USA) and maintained at 37–39°C using heating lamps under the surface of the surgical table when required. pH and arterial blood-gas tensions were measured using a blood-gas analyser (Radiometer ABL 3, Copenhagen, Denmark), and were maintained constant and also within the ranges of pH² 7.30–7.40, PaO₂ 4.4–5.5 kPa and PaCO₂ 22.7–28.0 kPa by adjusting ventilation and occasionally, when necessary, administration of small doses of sodium bicarbonate. HR, MAP and RSNA were recorded continuously on a multi-channel recording system.
system and stored on disk for later analysis (Macleb 8, ADInstruments, Australia). Concentrations of sevoflurane were measured with a Capnomac II (Datex, Helsinki, Finland).

RECORDING OF RSNA
The right kidney was exposed retroperitoneally by a left flank incision. A fascicle of the renal sympathetic nerves, alongside the renal artery, was isolated, desheathed and cut distally, immersed in a mineral oil pool and mounted on silver–silver chloride electrodes for recording sympathetic activity. Signals from sympathetic nerves were preamplified (Tektronix 122, Beaverton, OR) and displayed on an oscilloscope (Tektronix 565, Beaverton, OR), and also monitored by an audiorecorder. The amplified signals were rectified and integrated with a 100 ms time constant (Neurolog NL90, Hertfordshire, UK). Both amplified and integrated signals were displayed on an oscilloscope and plotted with a thermal recorder (Gould 1602, Essex, UK). The total electrical activity of the rectified and integrated signals during 20-s periods was measured in arbitrary units. Data for processing used the average of three measurements in each data set and were expressed as percentages of control values.

EXPERIMENTAL PROCEDURE
The preparation was allowed to stabilize for at least 30 min after completion of surgery. Twenty-two animals were allocated randomly to one of four groups. In group I (n = 7), sevoflurane (Abbott Laboratories Ltd, Queensborough, UK) was administered at 1.0%, 2.0%, 3.0% and 4.0% expired end-tidal concentrations, each for 20 min. In group II (n = 5), sevoflurane was administered as in group I but hypotension was prevented by infusion of angiotensin II 0.08–14 μg kg⁻¹ min⁻¹ (Sigma, Poole, Dorset, UK) and MAP was maintained within control values throughout. Measurements were made at the end of the 20-min period of administration at each concentration, and 30 min after sevoflurane withdrawal. Group III (n = 5) received infusion of 0.1% sodium nitroprusside (SNP) to lower MAP to 30–40 mm Hg after which it was discontinued. Observations of HR, MAP and RSNA were made every 5 min during infusions of SNP and also 30 min after it was discontinued. Subsequently, HR and RSNA data were collected from this group at MAP values comparable with those in group I induced by 1%, 2%, 3% and 4% sevoflurane and also after recovery. Animals in group IV (n = 5) were used to measure baroreflex sensitivity by observing pressor and depressor responses to bolus injections of phenylephrine 0.5, 1, 2 and 4 μg kg⁻¹ i.v. and SNP 2, 4, 8 and 16 μg kg⁻¹ i.v., respectively, to produce dose–response curves.

Maximum changes in HR (ΔHR), RSNA (ΔRSNA) and MAP (ΔMAP) in response to different pressor and depressor doses of phenylephrine and SNP, respectively, were observed during a control period and again 20 min after administration of 1% and 2% sevoflurane. Baroreflex sensitivity was evaluated by relating ΔHR or ΔRSNA and ΔMAP, and also by calculating the ratio of the maximum changes in HR and RSNA to the maximum changes in MAP (ΔHR/ΔMAP and ΔRSNA/ΔMAP) produced by the largest doses of SNP and phenylephrine.

ANALYSIS OF DATA
All data were expressed as mean (SEM). Statistical analysis was performed by analysis of variance (ANOVA) followed, where indicated, by paired t tests. P < 0.05 was considered to be statistically significant.

Results

HR, MAP AND RSNA
Examples of recordings of RSNA, from individual preparations, during administration of sevoflurane or SNP alone, and also during sevoflurane administration when a decrease in MAP was prevented by an infusion of angiotensin II, are shown in fig. 1.

The effects of sevoflurane and SNP on mean HR, MAP and RSNA are shown in fig. 2A and B. It can be seen that sevoflurane, which caused a reduction in mean MAP from 80 to 40 mm Hg at 4% sevoflurane, did not change mean RSNA with up to 3% sevoflurane which then decreased to 63% of control values at 4% sevoflurane (P < 0.05), without any significant change in mean HR from the mean control value of 246 beat min⁻¹. In contrast, when SNP induced a decrease in mean MAP from 80 to 40 mm Hg, there was an increase in mean HR from 249 to 292 beat min⁻¹ (P < 0.05) and mean RSNA by 150% of control.

The effects of sevoflurane on HR and RSNA when hypotension was prevented by an infusion of angiotensin II 0.08–14 μg kg⁻¹ min⁻¹ are shown in fig. 2C. It can be seen that mean MAP was maintained near 84 mm Hg (i.e. the control value), HR remained unchanged with up to 2% sevoflurane but decreased from the mean control value of 250 to 239 beat min⁻¹ and 231 beat min⁻¹ at 3% and 4% concentrations of sevoflurane, respectively (P < 0.05). Mean RSNA decreased significantly to 75% (P < 0.01), 65% (P < 0.01), 57% (P < 0.01) and 39% (P < 0.001) of mean control values at 1%, 2%, 3% and 4% sevoflurane, respectively.

BAROREFLEX SENSITIVITY
Typical examples of recordings during phenylephrine 4 μg kg⁻¹ i.v. and SNP 16 μg kg⁻¹ i.v. injections showing the effect of sevoflurane administration at 1 and 2% are illustrated in figure 3.

Dose–response curves for changes in mean HR and mean RSNA in response to the pressor and depressor effects of phenylephrine and SNP, respectively, are shown in fig. 4.

For further clarification, the effects of 1% and 2% sevoflurane on ΔHR/ΔMAP and ΔRSNA/ΔMAP at the maximum effect in response to the highest doses of phenylephrine (4 μg kg⁻¹) and SNP (16 μg kg⁻¹) are shown in fig. 5. It can be seen that 1% sevoflurane reduced mean ΔHR/ΔMAP and ΔRSNA/ΔMAP by 24% (ns) and 30% (P < 0.05) for the pressor effects of boluses of phenylephrine, and by 56% (P < 0.05) and 42% (P < 0.05) for the depressor effects of boluses of SNP, respectively; at 2% sevoflurane, the
mean responses to phenylephrine were reduced by 57% for \( \Delta HR/\Delta MAP \) \( (P < 0.01) \) and 36% for \( \Delta RSNA/\Delta MAP \) \( (P < 0.01) \) and responses to SNP were reduced by 81% for \( \Delta HR/\Delta MAP \) \( (P < 0.01) \) and 89% for \( \Delta RSNA/\Delta MAP \) \( (P < 0.01) \).

**Discussion**

In this study 1–4% sevoflurane caused a concentration-dependent decrease in mean arterial pressure (MAP), without any significant change in mean heart rate (HR) while mean renal sympathetic nerve activity (RSNA), which remained unchanged up to 3% sevoflurane, decreased by 37% with 4% sevoflurane. In contrast, hypotension induced by sodium nitroprusside (SNP) caused major increases in both HR and RSNA. When the decrease in MAP, and hence compensatory baroreflexes, was prevented by angiotensin II, sevoflurane caused a progressive concentration-related depression of RSNA, but a significant decrease in mean HR occurred only at the highest concentrations of 3% and 4% sevoflurane. Although it was shown that sevoflurane caused a major reduction in baroreflex responses, it was concluded that they continued to compensate for its depressant effect on RSNA and HR with concentrations of up to 3% and 4%, respectively.

Saeki and colleagues reported that RSNA in rabbits was not influenced during sevoflurane administration up to 1.25 MAC. A study in humans, in which direct recordings were made from nerve fibres in muscle sympathetic nerves, reported that the recorded activity remained unchanged during...
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administration of sevoflurane in concentrations ranging from 0.4 to 1.2 MAC.³ The results of our study showed that whereas concentrations of sevoflurane up to 3% (approximately MAC 1.5) caused no significant change in sympathetic activity, which is in keeping with previous work, a further increase to 4% (approximately 2 MAC) induced a significant reduction in RSNA.

Sevoflurane produced a concentration-related reduction in MAP, which is consistent with previous work.¹¹ Hypotension induced by sevoflurane results from both myocardial depression and a decrease in systemic vascular resistance.¹⁵ Whereas a reduction in MAP caused by SNP induces typical baroreflexes with an increase in both RSNA and HR, the reduction in MAP caused by sevoflurane is not associated with such a response. When angiotensin II was used to maintain MAP constant, to examine the effects of sevoflurane uncomplicated by baroreflexes, it was found that sevoflurane caused a concentration-related depression of both RSNA and HR. However, previously it has been shown that angiotensin II itself may induce a degree of modification of baroreflexes.⁷ For example the normal response to an increase in MAP, caused by peripheral vasoconstriction, is a decrease in both HR and sympathetic activity. During administration of angiotensin II in the rabbit, it has been shown that although there was a typical reduction in RSNA in response to the increase in arterial pressure,⁸ it occurred without a significant change in HR.⁷ In our study, when MAP was kept constant with angiotensin II, any observed changes in RSNA and HR could not be attributed to baroreflexes but indicated the unopposed direct effects of sevoflurane. Thus in the normal situation, without angiotensin II, a decrease in MAP would be expected to cause an increase in both RSNA and HR, which did not occur during sevoflurane administration in this study. However, although the studies when MAP was kept constant with angiotensin II clearly showed direct depression by sevoflurane of RSNA and HR, without further evidence one cannot comment on the degree of depression of the baroreflexes.

The effect of sevoflurane on baroreflexes was tested by observing the responses of RSNA and HR to the

Figure 3 Example recordings of typical changes in heart rate (HR), mean arterial pressure (MAP) and spontaneous sympathetic nerve activity (RSNA: lower traces, directly recorded activity; upper traces, rectified integral) produced by the largest bolus injections of sodium nitroprusside (SNP) 16 µg kg⁻¹ i.v. and phenylephrine (PE) 4 µg kg⁻¹ i.v. (arrows), before and after equilibration with 1% and 2% sevoflurane.

Figure 4 Relationship between ΔHR (A), ΔRSNA (B) and ΔMAP, caused by bolus injections of sodium nitroprusside (SNP) 2, 4, 8 and 16 µg kg⁻¹ i.v. and phenylephrine (PE) 0.5, 1, 2 and 4 µg kg⁻¹ i.v. before and after equilibration with sevoflurane in concentrations of 1.0% and 2.0% (mean (SEM), n = 5).
pressor and depressor effects of phenylephrine and SNP, respectively. It was demonstrated that baroreflex sensitivity, expressed as the relationship between changes in heart rate (ΔHR) and sympathetic activity (ΔRSNA), and MAP (i.e. ΔHR/ΔMAP and ΔRSNA/ΔMAP ratios) was increasingly attenuated by an increase in sevoflurane concentration. However, whereas in depressor tests the ΔHR/ΔMAP ratio was depressed significantly throughout by sevoflurane, in pressor tests this ratio became significantly depressed only at the higher concentration of 2% (P < 0.01, fig. 5). These findings would support the traditional concept of Glick and Braunwald who suggested that whereas responses to increases in arterial pressure predominantly involved parasympathetic cardiomotor vagal activity, responses to decreases in arterial pressure were mediated principally by changes in sympathetic activity.

In this study, the effect of sevoflurane at 3.0% and 4.0% on baroreflex sensitivity was not determined for two reasons. First, sevoflurane caused a major decrease in arterial pressure which prevented depressor tests without a serious risk to the viability of the preparations. Second, activity of the afferent fibres in the baroreceptor nerves is related to arterial pressure by sigmoid curves with the steepest part within the normal range of arterial pressures. This is reflected in rabbits in the relationship between RSNA and MAP which is also sigmoid and can be regarded as linear only for MAP values between 60 and 80 mm Hg. Responses to changes in MAP outside this range do not provide a basis for comparison.

It is not known if there are specific sites in the baroreflex pathways which are depressed by sevoflurane. Saeki and colleagues suggested that sevoflurane, enflurane and isoflurane may act by direct depression of the central nervous system (CNS) or transmission in sympathetic ganglia rather than changes, for example, in the sensitivity of the aortic baroreceptors themselves. Nevertheless, Seagaard and co-workers reported that baroreceptor sensitivity is increased by both isoflurane and halothane. From the data presented here it could be postulated that the absence of significant changes in RSNA at low concentrations of sevoflurane result from baroreflexes, albeit depressed, whereas the significant decrease in RSNA at higher concentrations is caused by direct depression of sympathetic pathways, for which the increasingly depressed baroreflexes can no longer compensate. Direct evidence of central depression was reported by Osawa and colleagues, who used the EEG to study the effect of sevoflurane on electrical activity in the CNS in cats and demonstrated that sevoflurane depressed the midbrain reticular neuronal activity in a concentration-dependent manner. Although it has been reported that both halothane and isoflurane depress transmission in sympathetic ganglia, as yet similar data have not been reported for sevoflurane.

In summary, although baroreflexes were depressed by sevoflurane, it appeared that they continued to compensate for the central depressant effects on RSNA up to concentrations of sevoflurane of 3% and cardiomotor activity up to 4%, which would provide an explanation for the apparent lack of effect of sevoflurane on the autonomic nervous system at low concentrations and validates the hypothesis tested in this study.

References