Comparison of the role of endothelin, vasopressin and angiotensin in arterial pressure regulation during sevoflurane anaesthesia in dogs

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Background. In this study we aimed to clarify the role of endothelin in arterial pressure regulation during anaesthesia with increasing concentrations of sevoflurane (1–3 MAC) and compare it with those of vasopressin and angiotensin.

Methods. After an awake control period, on different days, six dogs underwent each of the following four interventions: sevoflurane anaesthesia alone (1–3 MAC), sevoflurane after block of either endothelin receptors using tezosentan (3 mg kg⁻¹ followed by 3 mg kg⁻¹ h⁻¹), vasopressin V1a receptors using [d(CH₂)₅Tyr(Me²)]AVP (40 µg kg⁻¹) or angiotensin receptors using losartan (6 mg kg⁻¹ h⁻¹). Plasma concentrations of endothelin, big endothelin, vasopressin and renin were measured. Effects of sevoflurane in the presence and absence of the respective receptor block were analysed and compared using analysis of variance for repeated measures (ANOVA followed by Fisher’s PLSD (protected least significant difference) (P<0.05)).

Results. Mean arterial pressure decreased in a dose-dependent manner with sevoflurane during all interventions. At 1 MAC, this decrease was greatest during angiotensin receptor block (mean (SEM), −41 (3) mm Hg), intermediate during vasopressin and endothelin receptor block (−31 (4) and −30 (2) mm Hg respectively), and least during sevoflurane alone (−24 (3) mm Hg). The course of systemic vascular resistance mirrored the course of arterial pressure, while cardiac output did not differ between groups. Plasma concentrations of endothelin, big endothelin and renin did not change during any intervention, whereas vasopressin concentration increased from ~0.5 to 40 ng litre⁻¹ at 3 MAC as arterial pressure decreased in all groups.

Conclusions. At 1 MAC, angiotensin attenuated the decrease in arterial pressure during sevoflurane anaesthesia more than endothelin and vasopressin. However, at higher MAC only vasopressin was specifically activated to partly compensate for the arterial pressure decrease.

Br J Anaesth 2004; 92: 102–8

Keywords: anaesthetics volatile, sevoflurane; arterial pressure; hormones, antidiuretic, vasopressin; polypeptides, angiotensin; sympathetic nervous system, endothelin

Accepted for publication: July 28, 2003

Since the discovery of the endothelins¹ as the most potent vasoconstrictor peptides, there has been much effort to clarify their role in physiological and pathophysiological situations. Endothelin is involved in the local regulation of vasomotor tone and thus arterial pressure in the awake state in dogs.² Increased concentrations of endothelin occur during pathophysiological conditions such as septic shock in rats,³ essential and pulmonary hypertension and cardiac failure,⁴ and block of endothelin receptors has been suggested as a therapeutic option in these conditions.⁵ As endothelin receptor antagonists are on the rise as antihypertensive drugs,⁶ understanding the role of the endothelin system during anaesthesia is essential. For instance, during regional anaesthesia endothelin contributes to the maintenance of arterial pressure in dogs,⁷ and the increased plasma concentrations of endothelin during pharmacologically induced hypotension in dogs⁸ indicate that the endothelin system is activated during severe hypotension.
However, regarding inhalation anaesthesia, it is unknown whether and to what extent endogenous endothelin contributes to the maintenance of arterial pressure and whether the endothelin system is specifically activated to counterbalance further hypotension. In addition to endothelin, the endogenous peptides angiotensin and vasopressin should be considered, as both have been shown to be involved in arterial pressure regulation during inhalation anaesthesia in rats and humans.

Therefore, we studied whether endogenous endothelin is involved in the regulation of arterial pressure during inhalation anaesthesia, and compared the role of endothelin with those of angiotensin and vasopressin. For this purpose, we studied the effects of endothelin receptor blocker on haemodynamics during inhalation anaesthesia with sevoflurane compared with sevoflurane alone or sevoflurane after vasopressin or angiotensin receptor blocker.

Methods

The data were from 24 experiments on six trained dogs (Foxhounds of both sexes, weighing 28–35 kg) studied with approval of the District Governmental Animal Investigation Committee (Bezirksregierung Düsseldorf).

Several weeks before the experiments the dogs were operated under general anaesthesia (enflurane/nitrous oxide+fentanyl) and sterile conditions. For arterial pressure recording, baroreflex testing and blood sampling, both carotid arteries were exteriorized in skin loops. Ultrasound transit-time flow transducers (T101; Transonic Systems, Ithaca, NY) were implanted around the pulmonary artery for continuous recording of cardiac output (CO) and calibrated in vivo at least 3 weeks after implantation, as described previously. During convalescence the dogs were trained to lie quietly and unrestrained on their right side and to become familiar with the experimenters and the laboratory.

During the experiments the following variables were recorded continuously on an eight-channel polygraph (model RS 3800; Gould, Cleveland, OH, USA) and stored simultaneously on the hard disk of a conventional personal computer for further analysis after analogue-to-digital conversion at the rate of 1 kHz per channel.

Mean arterial pressure (MAP), carotid sinus pressure (CSP) and central venous pressure (CVP) were measured electromanometrically (Statham P-23ID, Elk Grove, IL, USA) through catheters in the carotid artery and in the superior vena cava. Correct position of the central venous catheter, which was advanced from the animal’s hind limb, was checked by fluoroscopy and adequacy of the venous pressure curve. Arterial pressure in the sinus of the carotid artery (CSP) was measured with a second catheter, which was advanced rostrally through the second exteriorized carotid artery. The electromanometers were referenced to the processus spinosus of the seventh cervical vertebra and calibrated with a mercury manometer. CO was measured continuously (see above), and systemic vascular resistance (SVR) was calculated as the quotient of (MAP–CVP) and CO.

To assess whether potential differences in arterial pressure between groups are modified by the arterial baroreflex, we measured the sensitivity of the carotid baroreflex sensitivity (BRS) as described previously. Both carotid arteries were occluded simultaneously for 45 s with self-made external cuff occluders, resulting in a decrease in CSP and an increase in heart rate. BRS was calculated as the quotient of changes in RR interval (ms) and CSP (BRS=ΔRR/ΔCSP).

We also measured intermittently arterial blood gas tensions, oxygen saturation and pH (ABL3; Radiometer, Copenhagen, Denmark).

During the respective experiments, endothelin was prevented from acting at its receptors by injecting tezosentan (3 mg kg⁻¹ followed by 3 mg kg⁻¹ h⁻¹; Actelion, Actelion Ltd, Allschwil, Switzerland), an endothelin receptor antagonist with high affinity for endothelin receptors ET₁ and ET₂. Vasopressin (V₁a) receptors were blocked by [d(CH₂)₅Tyr(Me²)]AVP (V-2255; Sigma Chemicals, Taufkirchen, Germany) at a dose of 40 μg kg⁻¹. Angiotensin-receptor block was achieved by infusing losartan (6 mg kg⁻¹ h⁻¹; MSD Sharp and Dohme, Haar, Germany), an angiotensin II receptor antagonist.

Completeness of receptor block was assessed during control experiments in awake animals by injecting 2.5 and 5 μg of endothelin–1 (E-7764; Sigma Chemicals), arginine-vasopressin 200 and 400 mU (V-0377; Sigma Chemicals) or angiotensin II 10 and 20 ng kg⁻¹ (A-9525; Sigma Chemicals). After injection of endothelin-1 5 μg, MAP increased by 22 (1) mm Hg but remained constant (1 (3) mm Hg) after previous receptor block. Similarly, vasopressin 400 mU increased MAP by 20 (2) mm Hg but remained constant at −2 (2) mm Hg after block of the vasopressin receptors.

Angiotensin II at a dose of 20 ng kg⁻¹ increased MAP by 15 (3) mm Hg but remained constant after losartan (1 (2) mm Hg).

To determine the plasma concentrations of vasopressin, endothelin, big endothelin and renin, arterial blood samples were collected at baseline and at the end of each intervention in chilled EDTA (ethylenediamine tetraacetate) tubes, which were immediately placed on crushed ice. Within 10 min, plasma was separated by centrifugation and stored at 20°C until analysis. Endothelin and big endothelin, a sensitive measure of activation of the endothelin system, were measured by enzyme immunoassay (endothelin, R&D Systems, Minneapolis, MN, USA; big endothelin, Biomedica, Vienna, Austria). Vasopressin was measured by radioimmunoassay (Bühlmann Laboratories, Allschwil, Switzerland). Renin concentrations were measured with a chemiluminescence immunoassay on a highly automated platform (Nichols Advantage®; Nichols Institute Diagnostics, San Clemente, CA, USA). Endothelin concentrations were not measured once tezosentan had been injected, as increased endothelin concentrations after...
tezosentan are caused by receptor displacement rather than by activation of the endothelin system. Vasopressin concentrations could not be determined once the vasopressin blocker had been injected because of cross-reactivity in the vasopressin immunoassay.

All experiments were carried out with awake dogs in basal metabolic state (food withheld for 12 h with free access to water) under standardized experimental conditions (dogs lying on their right side, lightly dimmed laboratory at a thermoneutral temperature for dogs (24°C)), always beginning at 8 a.m. During the experiments, dogs remained unrestrained on their right side on a cushioned table.

After connecting the animals to the recording system, we waited for ~30 min until haemodynamic variables had reached a steady state as the animals calmed down. The actual experiments started with baseline measurements for 30 min. Thereafter, the dogs were randomly assigned to one of the following four interventions. To maintain a minimum perfusion pressure during high concentrations of sevoflurane in the presence of the respective blockers, sevoflurane concentrations were restricted to maintain MAP above 35 mm Hg. Therefore, the highest sevoflurane concentrations were 2.5 MAC in the vasopressin–sevoflurane (AVP) group and 2.0 MAC in the angiotensin–sevoflurane (AT) group (see below).

In the sevoflurane (control) group (n=6), after baseline measurement in awake dogs, anaesthesia was induced with propofol 3 mg kg⁻¹ and a tracheal tube was inserted. Thereafter, the animals’ lungs were ventilated with oxygen-enriched air (FIO₂, 0.3) at a constant rate and, if necessary, tidal volume was adjusted to maintain normocarbia at higher MAC. Sevoflurane was added and immediately adjusted to an end-tidal concentration of 1 MAC (2 vol%) then to 2 and eventually to 3 MAC. Each anaesthetic concentration was maintained for 30 min, which was sufficiently long for the inspiratory and end-tidal concentrations to equilibrate.

In the endothelin–sevoflurane (ET) group (n=6), the endothelin receptor blocker was injected in awake animals to assess the role of endothelin during resting conditions. Thereafter, the same protocol was repeated, as during control conditions.

In the vasopressin–sevoflurane (AVP) group (n=6), the V₁a blocker was injected in awake animals to assess the role of vasopressin during resting conditions. Thereafter, the same protocol was repeated, as during the control condition. Sevoflurane concentrations applied were 1, 2 and 2.5 MAC.

In the angiotensin–sevoflurane (AT) group (n=6), the angiotensin receptor blocker was injected in awake animals to assess the role of the renin–angiotensin system during resting conditions. Thereafter, the same protocol was repeated as during control conditions. Sevoflurane concentrations applied were 1, 1.5, and 2 MAC.

To ensure complete elimination of sevoflurane and blockers, an interval of at least 1 week was interspaced between successive experiments in the same animal.

Data analysis and statistics
Data for all results are given as mean (SEM). Comparisons within each group were made using analysis of variance (ANOVA) for repeated measures. Comparisons between groups were made with the results obtained during the control condition and at 1 and 2 MAC of sevoflurane using repeated-measures ANOVA. If appropriate, Fisher’s PLSD (protected least significant difference) test was applied and statistical significance was assumed if P<0.05.

Results
Baseline measurements did not differ between study groups. With the onset of anaesthesia, arterial pressure decreased in all experimental groups to differing degrees: most in the AT group, less during AVP block and least during control conditions and in the ET group (P<0.05) (Fig. 1). At the end of the experiments, MAP values decreased to similar values (AT group: 34 (3), AVP group: 31 (1), control: 36 (3) and ET group: 33 (2) mm Hg); however, these values were reached at different MAC values: 2 MAC in the AT group, 2.5 in the AVP group and 3 MAC during control conditions and the ET group. Cardiac output decreased similarly in all experimental groups, with the exception of the AT group, in which cardiac output was reduced more (P<0.05). Changes in SVR resembled the course of MAP. SVR at low sevoflurane concentrations (1 MAC) was lowest in the AT group, and higher during the other interventions.

Above 1 MAC, SVR did not decrease further with the exception of the AVP group, in which SVR was reduced concentration-dependently to at least 20 (1) mm Hg litre⁻¹ min, indicating that, at high sevoflurane concentrations, only vasopressin is released to counterbalance a further decrease in SVR in order to partly compensate for a further arterial pressure reduction.

Plasma concentrations of vasopressin (Fig. 2), big endothelin, endothelin and renin yielded similar results. Whereas the concentrations of renin, endothelin and big endothelin were unchanged during each of the study conditions (data not shown), vasopressin concentrations increased from ~0.5 to ~40 ng litre⁻¹ at 3 MAC of sevoflurane in all groups. For comparison of the effect on MAP between groups elicited by sevoflurane in the presence of the respective blockers, changes in arterial pressure at 1 MAC of sevoflurane in comparison with the respective controls were calculated. Sevoflurane 1 MAC was chosen for comparison, because at this anaesthetic concentration the vasopressin system was not activated, so that a meaningful comparison of the effects of the blockers during anaesthesia was feasible, i.e. without the compensatory actions of increased vasopressin concentrations. With the transition from awake to 1 MAC of sevoflurane, arterial pressure decreased least with sevoflurane given alone (~24 (3) mm Hg), to an intermediate degree in the presence of endothelin and vasopressin receptor block (~31 (4) and ~30
**Fig 1** Time course of arterial pressure (MAP), cardiac output (CO) and systemic vascular resistance (SVR) in the awake state and during sevoflurane anaesthesia (1–3 MAC) alone or after pretreatment with an endothelin (ET), vasopressin (AVP) or angiotensin (AT) receptor antagonist. Mean (SEM) from six dogs in each group. Asterisks indicate $P<0.05$ compared with control conditions; crosses indicate $P<0.05$ for comparisons between groups (values included: control, 1 and 2 MAC).

**Fig 2** Plasma concentrations of vasopressin in the awake state and during sevoflurane anaesthesia (1–3 MAC) alone or after pretreatment with an endothelin (ET) or angiotensin (AT) receptor antagonist. Mean (SEM) from six dogs in each group. $P<0.05$ for all vasopressin plasma concentrations when sevoflurane concentration was $\geq 2$ MAC in all groups compared with control conditions, with no difference between groups.
The changes in arterial pressure were not related to differences in the sensitivity of the arterial baroreflex, either during awake conditions or during sevoflurane anaesthesia, as baroreflex sensitivity (which was ~7 ms mm Hg⁻¹ during baseline conditions and in the presence of the blockers) was almost completely suppressed during anaesthesia, with no difference between groups.

Oxygen saturation, pH, PO₂ and PCO₂ were in the physiological range during awake conditions and remained so during sevoflurane anaesthesia up to 3 MAC, except for pH, which decreased at higher MAC, resulting mainly from the slightly increased PCO₂ (Table 1).

Discussion

Our results show that, during sevoflurane anaesthesia (1–3 MAC), endogenous endothelin, renin and vasopressin attenuate the decrease in MAP. However, the increase in plasma vasopressin concentrations during high sevoflurane concentrations while big endothelin, endothelin and renin concentrations remain unchanged indicates that only endogenous vasopressin is specifically activated to partly compensate for a further decrease in MAP.

Discussion of the methods

Our conclusions rest upon a sufficient block of the endothelin–, vasopressin– or renin–angiotensin system and comparable conditions in the same dog during repetitive experiments. The endothelin and vasopressin receptor block has been discussed in detail previously. Losartan is a specific angiotensin II receptor antagonist and is appropriate for the elimination of the vasoconstriction elicited by the renin–angiotensin system as it antagonizes the final mediator of this vasoconstrictor system. The dosage used in our study is comparable to that used by others in conscious dogs. Moreover, angiotensin II at the dose of 20 ng kg⁻¹ increased MAP by ~15 mm Hg, an effect which was abolished after losartan pretreatment in control experiments (data not shown).

Therefore, from a methodological point of view, the chosen dosages of the vasopressin, endothelin and angiotensin receptor antagonists should have been appropriate to block the respective receptors sufficiently.

Discussion of the results

Hypotension during inhalation anaesthesia may be caused by several factors, e.g. by a decrease in cardiac output and systemic vascular resistance. In our experiments, both factors contributed significantly to the reduction of arterial pressure, except at 3 MAC, where SVR reverted to control levels. During angiotensin-receptor block cardiac output was reduced more when compared with the control group, which may partially explain the fact that the lowest arterial pressure occurred in the AT group, but not the differences between the other experimental groups. Changes in baroreflex sensitivity can likewise be excluded as a cofactor because it was almost completely suppressed during sevoflurane anaesthesia at 1 MAC. Therefore, differences in arterial pressure between groups in our study are related mainly to different levels of vasoconstriction (systemic vascular resistance).

The physiological role of endogenous endothelin in the regulation of arterial pressure has long been unclear; for instance, in anaesthetized dogs endothelin receptor block did not change arterial pressure. However, it is now accepted that endogenous endothelin does contribute to arterial pressure regulation under resting conditions, because block of its receptors decreased arterial pressure in healthy volunteers and awake dogs. Consistent with our experiments, this was accompanied by a small decrease in SVR, a measure of vasomotor tone. This may be explained by the fact that resistance arteries, which are the main determinants of vasomotor tone, are particularly

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(2) mm Hg respectively), and most after angiotensin receptor blocker (~41 (3) mm Hg).
sensitive to the effects of endothelin.\(^{21}\) In contrast, the role of endothelin in partly compensating for hypotension is unclear, but the fact that endogenous endothelin is activated during severe hypotension\(^{8}\) indicates a role for endothelin in the stabilization of arterial pressure also during inhalation anaesthesia. This, however, is only partially confirmed by our own study because the decrease in arterial pressure attributable to the administration of 1 MAC sevoflurane was larger in the presence of endothelin receptor block compared with sevoflurane alone, but concentrations of neither big endothelin nor endothelin increased with severe hypotension. Thus, endothelin attenuates the drop in arterial pressure during sevoflurane anaesthesia to some extent, but the endothelin system is not specifically activated to compensate for further hypotension.

Likewise, renin–angiotensin partly compensated for the decrease in MAP during inhalation anaesthesia with sevoflurane, but to an even greater extent, as arterial pressure decreased most in the presence of angiotensin receptor block (–41 (3) mm Hg). This result is in accordance with other experiments in which hypotension was more severe during isoflurane anaesthesia after an angiotensin II receptor blocker was given in rats\(^9\) and humans.\(^{11}\) Again in parallel to the endothelin system, even the renin–angiotensin system is not additionally activated to compensate further for arterial pressure reductions, as indicated by the unchanged renin concentrations during all interventions. This, however, contrasts with other experiments in which renin activity increased during 1.5 MAC of desflurane and isoflurane anaesthesia.\(^{10}\) However, activation of the renin–angiotensin system depends mainly on the integrity of the sympathetic nervous system, which is activated only during anaesthesia with isoflurane and desflurane,\(^{22}\) whereas all other inhalation anaesthetics concentration-dependently suppress sympathetic activity.\(^{23}\) Nevertheless, the renin–angiotensin system was the main contributor to arterial pressure in our experiments.

In contrast, vasopressin shows different properties and contributes little to arterial pressure during physiological conditions. Most of its direct vascular actions are buffered by baroreflexes and are only unmasked after baroreceptor denervation\(^{24}\) or after destruction of the central nervous system.\(^{25}\) In accordance with our results, block of only the V\(_{1a}\) receptors failed to demonstrate cardiovascular effects in dogs\(^{26}\) and humans.\(^{27}\) During low concentrations of sevoflurane, i.e. at 1 MAC, vasopressin concentrations did not increase, indicating that arterial pressure has to fall below a certain level before vasopressin release is activated. Accordingly, at 1 MAC, a concentration at which the vasopressin system is not activated, the additional arterial pressure decrease during receptor block (angiotensin and endothelin) results solely from the respective receptor block, which was the rationale for our decision to compare arterial pressure effects at this MAC. At higher MAC, however, vasopressin concentrations increased while arterial pressure decreased. This is in accordance with the view that, during hypotensive challenges, vasopressin release is activated, as indicated by the increase in plasma vasopressin concentrations, not only in our experiments during inhalation anaesthesia but also during epidural anaesthesia\(^1\) and during haemorrhage.\(^{28, 29}\) The control and release of endogenous vasopressin depends on cardiopulmonary afferents being sensitive to heart volume\(^{28}\) and on arterial baroreceptors.\(^{30}\) The absence of vasopressin release after sinoaortic denervation during graded hypotension,\(^3\) in contrast to an unchanged increase in vasopressin after sole cardiopulmonary denervation, indicates that sinoaortic receptors are the main regulators of vasopressin release. This observation contrasts in part with our own, in which the sensitivity of the arterial baroreflex was almost eliminated at 1 MAC of sevoflurane. However, this result indicates only that the suppressed regulation of heart rate (baroreflex) is independent of the vasopressin-mediated regulation of arterial pressure to prevent severe hypotension.

**Clinical implications**

The results of our study are of potential interest to clinicians because antagonists of endothelin, angiotensin and perhaps vasopressin receptors are already commonly used or are on the rise as antihypertensive drugs. Accordingly, if inhalation anaesthesia is performed in patients receiving such agents, they are likely to expect severe hypotension, which has already been shown in patients receiving an angiotensin receptor antagonist.\(^1\) However, this effect should be less for vasopressin and endothelin blockers. Moreover, our study provides additional information about which of these blockers should be continued (or not) before inhalation anaesthesia is performed.

Regardless of this speculation, we have shown for the first time that during inhalation anaesthesia with sevoflurane the endogenous vasoconstrictors endothelin, angiotensin and vasopressin compensate to different extents for the drop in arterial pressure in dogs. However, only vasopressin is additionally released to counteract a further decrease in arterial pressure, and thus to avoid more severe hypotension.

**Acknowledgements**

We wish to thank Dr Martine Clozel, Actelion Ltd, for kindly providing us with the endothelin receptor antagonist, and MSD Sharp & Dohme for providing the angiotensin receptor antagonist.

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