Endothelin-A Receptor Blockade Does Not Debilitate the Cardiovascular and Hormonal Adaptation to Xenon or Isoflurane Anesthesia in Dogs

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The objective of this study was to investigate whether circulatory and hormonal changes during xenon plus remifentanil or isoflurane plus remifentanil anesthesia are altered by endothelin-A (ET_A) receptor blockade. Eight beagle dogs were studied in four protocols ($n = 7$ each). After a 30-min awake period, anesthesia was induced with 8 mg/kg propofol, administered intravenously (iv), and maintained with either 0.8% ± 0.01% (vol/vol) isoflurane plus 0.5 μg/kg/min remifentanil (Protocol 1) or 63% ± 1% (vol/vol) xenon plus 0.5 μg/kg/min remifentanil (Protocol 2) for 1 hr. Protocols 3 and 4 were preceded by ET_A blockade with ABT-627 (Atrasentan; iv bolus of 1 mg/kg, then 100 μg/kg/h continuously). Irrespective of Atrasentan administration, the mean arterial blood pressure (MAP) ranged between 92 and 96 mm Hg in the awake state and fell to 67 ± 3 mm Hg in controls (mean ± SEM) and to 64 ± 2 mm Hg in the Atrasentan group during isoflurane plus remifentanil anesthesia, whereas MAP remained constant during xenon plus remifentanil anesthesia. A decrease in heart rate was observed during either kind of anesthesia, but bradycardia was most prominent during xenon plus remifentanil anesthesia. In the control groups, and in the Atrasentan-treated dogs, a decrease in cardiac output and an increase in systemic vascular resistance were more prominent during xenon plus remifentanil than during isoflurane plus remifentanil anesthesia. Hormonal alterations during anesthesia remained unaffected by ET_A receptor blockade. Angiotensin II and vasopressin increased in all protocols, and adrenaline and noradrenaline concentrations rose only during xenon plus remifentanil anesthesia. We conclude that the hemodynamic and hormonal adaptation after xenon plus remifentanil and isoflurane plus remifentanil anesthesia does not depend on the endothelin system, because it is unaffected by ET_A receptor inhibition. Therefore, the use of Atrasentan does not impair cardiovascular stability during xenon- or isoflurane-based anesthesia in our dog model. However, the way anesthesia is performed is of crucial importance for hemodynamic and hormonal reactions observed during research in animals because the release of vasopressin and catecholamines may be intensified by xenon plus remifentanil anesthesia. Exp Biol Med 231:834–839, 2006

Key words: cardiovascular; Atrasentan; renin-angiotensin system; vasopressin; catecholamines; beagle

Introduction

Acute or prolonged hypotensive episodes during the induction and maintenance of anesthesia are frequently observed, especially in patients with cardiovascular diseases, because the hemodynamic regulation during anesthesia depends greatly on an intact interaction of the sympathetic nervous system and vasoactive hormones such as adrenaline and noradrenaline, vasopressin, endothelins, and angiotensin II (1–3). An important effect of these hormones is to limit the anesthesia-induced decrease in mean arterial pressure (MAP), systemic vascular resistance and cardiac output (CO), and to defend the perfusion of vital organs and tissues (4). However, chronic antihypertensive medication or the treatment of some other underlying cardiovascular disease itself may deteriorate the physiologic hemodynamic adaptation to anesthesia. For instance, angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists can aggravate the hypotensive effect of anesthetics, leading to severe hypotension (1, 2).

During the past few years, endothelin receptor antagonists have been evaluated for a range of clinical

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applications, such as the treatment of pulmonary hypertension and acute heart failure (5–7). Therefore, in the future, the number of patients chronically treated with endothelin receptor antagonists will likely increase. However, under chronic treatment, we cannot act on the assumption of an intact neurohumoral system.

On the other hand, cardiovascular impairment during anesthesia depends largely on the specific anesthetic drug chosen. The noble gas, xenon, a modern anesthetic (8, 9), seems to lack negative cardiovascular effects because blood pressure and left ventricular performance have been shown to be only minimally affected during xenon anesthesia in dogs (10), pigs (11), and humans (12, 13). Therefore, the present study was performed to investigate whether endothelin-A (ET_A) receptor inhibition impairs the short-term hemodynamic and hormonal adaptation to anesthesia maintained either with isoflurane plus remifentanil or with xenon plus remifentanil. We investigated acute short-term effects that occur within 1 hr of anesthesia.

Materials and Methods

The study was approved by the local Governmental Animal Protection Committee (G0424/99) and conforms to the United States Guidelines on the Care and Use of Laboratory Animals (14).

Eight healthy pure-bred female beagle dogs (body weight, 14.0 ± 1.4 kg) were kept under standardized environmental conditions and received a dietary regimen that was calculated for sodium, potassium, and water intake, as described previously (15).

Before the start of the experiment, an arterial line (20 G, No. 4235–8; Ohmeda, Erlangen, Germany) was advanced into the abdominal aorta *via* the femoral artery, and a pulmonary artery catheter (5F, No. 132F5; Baxter, Unterschleissheim, Germany) was inserted *via* the right external jugular vein. For both procedures, local anesthesia (5 ml of 1% lidocaine; Braun, Melsungen, Germany) was applied. The catheters were used for continuous blood pressure monitoring in the systemic circulation and the pulmonary artery, CO measurements, and blood sampling.

Experimental Protocols. A total of 28 experiments were performed in random order in four different protocols ($n = 7$ each).

After a baseline period of 30 mins in an awake dog, anesthesia was induced with intravenous (iv) administration of 8–10 mg/kg propofol (1% Disoprivan, lipid emulsion; AstraZeneca GmbH, Wedel, Germany). After induction, the dog's trachea was intubated with a cuffed Woodbridge tube (34–36 Charrière) and mechanically ventilated on a closed circuit system (PhysioFlex; Dräger Medical, Lübeck, Germany). The ventilator was set to a respiratory rate of 12 breaths/min and a positive end-expiratory pressure of 4 mm Hg. The tidal volume was adjusted to keep the arterial carbon dioxide tension between 35 and 40 mm Hg. Tidal volume ranged between 208 and 223 ml, resulting in a minute volume of approximately 2.5 L/min and a peak airway pressure of 14–15 cm H_2O. General anesthesia was maintained for 1 hr to assess the short-term adaptation to different forms of anesthesia as follows:

Protocol 1 (Isoflurane Plus Remifentanil). End-tidal isoflurane concentration of 0.8% ± 0.01% (vol/vol) in oxygen/air with an inspiratory oxygen concentration of 26 ± 1%, plus 0.5 μg/kg/min remifentanil.

Protocol 2 (Xenon Plus Remifentanil). End-tidal xenon concentration of 63% ± 1% (vol/vol) with an inspiratory oxygen concentration of 29% ± 1%, plus 0.5 μg/kg/min remifentanil.

Protocol 3 (Isoflurane Plus Remifentanil, ET_A Blockade) and Protocol 4 (Xenon Plus Remifentanil, ET_A Blockade). The same as Protocols 1 and 2, but ET_A receptor inhibition was induced 20 mins before the baseline awake period by iv administration of ABT-627 (Atrasentan; bolus of 1 mg/kg, then 100 μg/kg/h continuous).

Hemodynamics were recorded continuously. At the end of the awake period, as well as after 1 hr of anesthesia, blood samples for the determination of plasma hormones were taken, and CO was measured by thermodilution.

All values are means ± SEM ($n = 7$). A general linear model of analysis of variance (GLM ANOVA) for repeated measures was applied. *Post-hoc* testing was performed with Student's *t* test. The level of significance for the error of first order was adjusted according to the Holm procedure (16). Statistical significance was assumed at $P < 0.05$.

Results

Irrespective of Atrasentan administration, MAP (Table 1) ranged between 92 and 96 mm Hg in the awake state, and fell to 67 ± 3 (mean ± SEM) in the control group and to 64 ± 2 mm Hg in the Atrasentan group during isoflurane plus remifentanil anesthesia, respectively. MAP remained constant during xenon plus remifentanil anesthesia. A decrease in heart rate (Table 1) was observed during anesthesia with or without ET_A inhibition, but bradycardia was most prominent in dogs anesthetized with xenon plus remifentanil. In control dogs, as well as in ET_A-inhibited dogs, a decrease in CO (Table 1) and an increase in systemic vascular resistance (Table 1) were more prominent during xenon plus remifentanil than during isoflurane plus remifentanil anesthesia. This matches a reduction in CO by 47% and 61% in the control dogs, and 52% and 59% in ET_A-inhibited dogs, respectively. Stroke volume (Table 1) decreased slightly during anesthesia and was similar in all protocols. Central venous and pulmonary capillary wedge pressure (Table 1) were higher in anesthetized than in awake animals, and xenon plus remifentanil induced significantly higher filling pressures than isoflurane plus remifentanil; this did not depend on ET_A inhibition. Irrespective of ET_A inhibition, pulmonary vascular resistance (Table 1) rose during both forms of anesthesia, whereas an increase in pulmonary artery pressure could only be observed during xenon plus remifentanil administration.

Table 1. Hemodynamic Parameters[a]

	Controls		ET_A blockade	
	Awake	Anesthesia	Awake	Anesthesia
Heart rate (bpm)				
Isoflurane/remifentanil	77 ± 5	54 ± 2*,**	78 ± 3	52 ± 2*,**
Xenon/remifentanil	86 ± 4	40 ± 3*	91 ± 6	41 ± 2*
Mean arterial pressure (mm Hg)				
Isoflurane/remifentanil	95 ± 2	67 ± 3*,**	92 ± 4	64 ± 2*,**
Xenon/remifentanil	96 ± 4	85 ± 6	94 ± 1	87 ± 6
Cardiac output (L/min)				
Isoflurane/remifentanil	2.3 ± 0.2	1.2 ± 0.1*,**	2.2 ± 0.1	1.1 ± 0.1*,**
Xenon/remifentanil	2.3 ± 0.2	0.9 ± 0.1*	2.4 ± 0.1	0.9 ± 0.1*
Stroke volume (ml)				
Isoflurane/remifentanil	29 ± 2	23 ± 2*	29 ± 2	22 ± 1*
Xenon/remifentanil	27 ± 2	23 ± 2*	27 ± 1	23 ± 1*
Central venous pressure (cm H_2O)				
Isoflurane/remifentanil	1 ± 1	3 ± 0.6*,**	1 ± 0.4	2 ± 0.3*,**
Xenon/remifentanil	3 ± 0.8	8 ± 1.2*	3 ± 1.0	8 ± 0.7*
Pulmonary capillary wedge pressure (mm Hg)				
Isoflurane/remifentanil	1 ± 0.3	3 ± 0.4*,**	1 ± 0.3	4 ± 0.1*,**
Xenon/remifentanil	2 ± 0.7	9 ± 0.9*	3 ± 1.0	9 ± 0.9*
Mean pulmonary artery pressure (mm Hg)				
Isoflurane/remifentanil	12 ± 1	11 ± 1**	11 ± 1	11 ± 1**
Xenon/remifentanil	12 ± 1	16 ± 1*	12 ± 1	15 ± 1*
Systemic vascular resistance (dyn · s/cm^5)				
Isoflurane/remifentanil	3387 ± 309	4443 ± 369*,**	3367 ± 224	4383 ± 235*,**
Xenon/remifentanil	3282 ± 281	7231 ± 803*	3054 ± 134	7030 ± 888*
Pulmonary vascular resistance (dyn · s/cm^5)				
Isoflurane/remifentanil	376 ± 52	557 ± 24*	356 ± 39	513 ± 54*
Xenon/remifentanil	365 ± 54	652 ± 55*	310 ± 50	540 ± 62*

[a] Values are presented as means ± SEM; $n = 7$. Values were measured during a 30-min awake period, after 60 mins anesthesia in controls, and after ET_A receptor inhibition.
*$P < 0.05$ versus awake; **$P < 0.05$ versus xenon/remifentanil.

All hemodynamic values that were measured continuously (arterial blood pressure, pulmonary blood pressure, central venous pressure, and heart rate) were similar with and without ET_A inhibition at 1 hr of anesthesia and throughout the time course of the experiment.

Oxygen delivery (Table 2) was comparable between the different anesthesia protocols with and without ET_A inhibition, and declined during anesthesia. Oxygen consumption decreased during isoflurane plus remifentanil administration only, and was kept constant during xenon plus remifentanil anesthesia, in which the oxygen extraction (Table 2) increased to a higher extent than during isoflurane plus remifentanil administration. Oxygen delivery, consumption, and extraction were not altered by ET_A receptor inhibition.

Hormonal alterations during anesthesia remained unaffected by ET_A receptor blockade (Fig. 1), except for endothelin-1 concentrations, which were slightly higher during ET_A inhibition in the xenon plus remifentanil–anesthetized dogs. Angiotensin II and vasopressin increased in all protocols, whereas adrenaline and noradrenaline concentrations rose only during xenon plus remifentanil anesthesia (Fig. 1).

Blood gases, pH, base excess, arterial lactate concentrations, and plasma electrolytes were within normal limits in all protocols and did not vary with and without ET_A receptor inhibition (data not shown).

Discussion

The present study was performed to investigate whether ET_A receptor inhibition impairs the short-term hemodynamic and hormonal adaptation to anesthesia maintained either with isoflurane plus remifentanil or with xenon plus remifentanil administration.

We found that ET_A receptor inhibition:

1. Does not alter baseline hemodynamics in awake, healthy dogs before anesthesia.
2. Does not impair the hemodynamic adaptation, nor the increase of angiotensin II, vasopressin, and catecholamine concentrations pertinent to isoflurane plus remifentanil or xenon plus remifentanil anesthesia.
3. Does not prevent the increase in mean pulmonary artery pressure (MPAP) observed during xenon plus remifentanil anesthesia.
4. Can, therefore, be safely used during isoflurane plus remifentanil and xenon plus remifentanil anesthesia, with respect to hemodynamics and cardiovascular hormones, in our dog model.

Table 2. Oxygen Consumption, Delivery, and Extraction[a]

	Controls		ET_A blockade	
	Awake	Anesthesia	Awake	Anesthesia
$\dot{V}O_2$ (ml/min)				
Isoflurane/remifentanil	84 ± 7	57 ± 3*	72 ± 8	53 ± 4*
Xenon/remifentanil	74 ± 8	60 ± 3	68 ± 9	62 ± 5
$\dot{D}O_2$ (ml/min)				
Isoflurane/remifentanil	408 ± 51	181 ± 17*	397 ± 42	190 ± 13*
Xenon/remifentanil	407 ± 44	175 ± 14*	423 ± 35	188 ± 20*
$C_{(a-v)}O_2$ (ml/dl)				
Isoflurane/remifentanil	3.7 ± 0.2	4.9 ± 0.4**	3.2 ± 0.3	4.7 ± 0.2*,**
Xenon/remifentanil	3.3 ± 0.4	6.9 ± 0.5*	2.8 ± 0.4	6.7 ± 0.5*

[a] Values are presented as means ± SEM; $n = 7$. Values were measured during a 30-min awake period and after 60 mins of anesthesia. $\dot{V}O_2$, total body oxygen consumption; $\dot{D}O_2$, total body oxygen delivery; $C_{(a-v)}O_2$, difference of arterial to mixed venous oxygen content.
*$P < 0.05$ versus awake; **$P < 0.05$ versus xenon/remifentanil.

During anesthesia, there was a pronounced activation of cardiovascular hormones, which was not altered by ET_A receptor blockade, except for endothelin-1 plasma concentrations, which slightly increased after ET_A blockade as compared with the control group. This is a common finding in dogs and humans (15, 17), and has been attributed to the inhibition of a negative feed-back mechanism and/or displacement of endothelin-1 from the ET_A receptor (18). In a previous study on dogs of the same breed, we have shown that this dose of Atrasentan is selective for ET_A (15). The anesthesia-induced increase of endothelin-1 was most prominent during xenon plus remifentanil administration, with and without ET_A blockade. Therefore, our data suggest that xenon facilitates the release of endothelin-1. However, plasma concentrations might not appropriately reflect the stimulation of a paracrine/autocrine hormone such as endothelin-1.

The activation of the renin-angiotensin system, as reflected by the increase in angiotensin II plasma concentrations during both anesthesia protocols, can be caused by intra-renal stimuli—such as the barostat and/or macula densa mechanisms, and/or by extra-renal stimuli *via* renal nerves and elevated plasma concentrations of adrenaline and noradrenaline (19). Interestingly, during xenon plus remifentanil anesthesia, angiotensin II plasma concentrations rose in the face of unaltered arterial blood pressure, which can likely be explained by extra-renal stimuli on renin release, such as plasma catecholamines.

Indeed, similar to a previous study of our laboratory (unpublished data), there was a 4-fold increase in adrenaline and a 12-fold increase in noradrenaline concentrations during xenon plus remifentanil anesthesia in the control group. This increase was hardly attenuated by ET_A blockade. The exaggerated increase of plasma catecholamines during xenon plus remifentanil anesthesia could be attributed to its inhibitory effect on *N*-methyl-D-aspartate (NMDA) receptors. Ketamine, another anesthetic drug, for instance, is involved in the release, metabolism, and reuptake of adrenaline and noradrenaline because of its inhibitory effect on NMDA receptors (20). Xenon shares this inhibitory action with ketamine and, therefore, could be similarly involved in catecholamine release (21–23) and could account for the large increase observed in our study. Interestingly, ET_A blockade did not alter catecholamine concentrations during anesthesia. This is in contrast to a previous study of our laboratory on the same breed of dogs (15), in which the release of catecholamines was investigated in response to acute hemorrhage. In that study, it was proposed that endogenous endothelin-1, *via* ET_A receptors, does substantially contribute to the release of adrenaline, and that ET_A blockade disinhibits noradrenaline release after hemorrhage. Conclusively, anesthesia-induced catecholamine release is completely different from hemorrhage-induced stimulation, and probably subject to different regulatory mechanisms.

It is of interest that isoflurane plus remifentanil anesthesia impairs the sympathetic nervous system in such a way as to prevent any increase in adrenaline and noradrenaline. This may, in part, account for the hemodynamic impairment during isoflurane plus remifentanil discussed in the second paragraph below.

Vasopressin concentrations increased to vasopressor concentrations during isoflurane plus remifentanil anesthesia, which is most likely caused by the decrease in arterial blood pressure because plasma osmolarity and acid-base status (data not shown) remained constant. During xenon plus remifentanil anesthesia, however, the distinct stimulation of the sympathetic nervous systems has to be taken into account and may explain the exaggerated rise in vasopressin concentrations.

Concerning the hemodynamic alterations after anesthesia, there was virtually no difference between ET_A-antagonized and untreated dogs. Isoflurane plus remifentanil anesthesia resulted in a severe cardiovascular depression with reduced arterial pressure and CO. The sympathetic nervous system was found to be suppressed because neither adrenaline nor noradrenaline increased to maintain arterial pressure and/or CO. However, xenon plus remifentanil

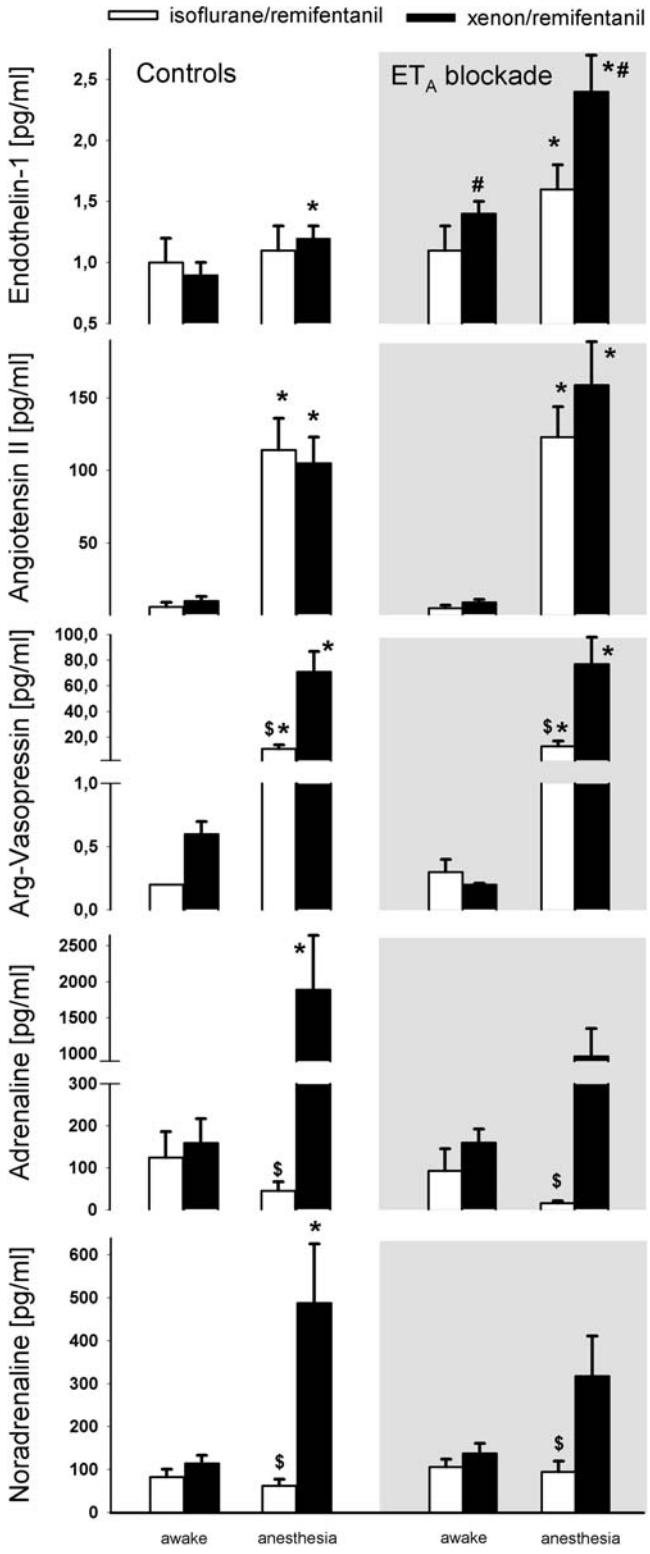

Figure 1. Plasma concentrations of endothelin-1, angiotensin II, arg-vasopressin, adrenaline, and noradrenaline in awake dogs and after 60 mins of anesthesia with (gray background) and without ET_A receptor inhibition. Values are presented as means ± SEM; $n = 7$. *$P < 0.05$ versus awake; \$$P < 0.05$ versus xenon plus remifentanil; #$P < 0.05$ versus controls.

anesthesia was associated with extraordinarily high vasopressor hormone concentrations (vasopressin, adrenaline, and noradrenaline); in the systemic circulation, the increase in vasopressors acted to maintain arterial pressure by a steep increase in systemic vascular resistance. Similarly, in the pulmonary circulation, vascular resistance increased and caused MPAP to increase during xenon plus remifentanil, but not during isoflurane plus remifentanil anesthesia. Finally, because of vasopressor effects on venous capacitance vessels, central venous and pulmonary capillary wedge pressures were higher during xenon plus remifentanil than during isoflurane plus remifentanil anesthesia. Part of the central venous and pulmonary capillary wedge pressure increase must be attributed to positive end-expiratory pressure ventilation.

Interestingly, the increase in MPAP observed during xenon plus remifentanil anesthesia could not be prevented by ET_A receptor inhibition. It might be speculated that the vasodilatory effect of ET_A receptor blockade in the pulmonary circulation is abolished by extraordinarily high plasma catecholamine concentrations. However, we have to relativize and bear in mind that the rise in MPAP was very small and still resulted in a physiologic pressure range.

In summary, we conclude that specific ET_A receptor inhibition with Atrasentan does not significantly alter hormonal and hemodynamic alterations after anesthesia in our dog model. This is true for isoflurane plus remifentanil, as well as for xenon plus remifentanil anesthesia, two forms of anesthesia with quite opposite hemodynamic and hormonal implications. Therefore, Atrasentan can be safely used during both kinds of anesthesia.

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