Desflurane increases heart rate independent of sympathetic activity in dogs

O. Picker, L. A. Schwarte, A. W. Schindler, T. W. L. Scheeren

Heinrich-Heine-University, Department of Anaesthesiology, Düsseldorf, Germany

Summary

Background and objective: Desflurane has been shown to increase sympathetic activity and heart rate (HR) in a concentration-dependent manner. Nevertheless, desflurane, like all other volatile anaesthetics, increased HR in parallel to vagal inhibition in a previous study. Therefore, our hypothesis is that desflurane elicits tachycardia by vagal inhibition rather than by activation of the sympathetic nervous system.

Methods: Six dogs were studied awake and during desflurane anaesthesia (1 and 2 MAC) alone, after pre-treatment with propranolol (2 mg kg\(^{-1}\) followed by 1 mg kg\(^{-1}\) h\(^{-1}\)), or after pre-treatment with atropine (0.1 mg kg\(^{-1}\) followed by 0.05 mg kg\(^{-1}\) h\(^{-1}\)). The effects on HR and HR variability were compared by an analysis of variance (\(P < 0.05\)). HR variability was analysed in the frequency domain as power in the high-frequency range (0.15–0.5 Hz, vagal activity) and low-frequency range (0.04–0.15 Hz, sympathetic and vagal activity).

Results: HR increased during 2 MAC of desflurane from about 60 (awake) to 118 ± 2 beats min\(^{-1}\) (mean ± SEM) in controls and to 106 ± 3 beats min\(^{-1}\) in dogs pre-treated with propranolol. In contrast, pre-treatment with atropine increased HR from 64 ± 2 to 147 ± 5 beats min\(^{-1}\) (awake) and HR decreased to 120 ± 5 beats min\(^{-1}\) after adding desflurane. High-frequency power correlated inversely with HR (\(r^2 = 0.95/0.93\)) during desflurane alone and in the presence of \(\beta\)-adrenoceptor blockade, with no significant difference between regression lines. There was no correlation between these variables during atropine/desflurane.

Conclusions: The increase in HR elicited by desflurane mainly results from vagal inhibition and not from sympathetic activation.

Keywords: ANAESTHETICS, INHALATION; PARASYMPATHETIC NERVOUS SYSTEM; SYMPATHETIC NERVOUS SYSTEM.
not change during desflurane anaesthesia [8]. Desflurane, like all other volatile anaesthetics, decreases HR in a concentration-dependent fashion in isolated hearts [9].

Our aim was to clarify the role of the sympathetic nervous system on the HR increase during desflurane anaesthesia. For this purpose, we studied the effects of desflurane on HR in intact dogs and after blockade of sympathetic or vagal activities, respectively.

Methods
Six trained dogs (foxhounds of both sexes, weighing 24–34 kg) were studied with approval of the District Governmental Animal Investigation Committee. Several weeks before the actual experiments the dogs were operated upon under general anaesthesia (enflurane/nitrous oxide + fentanyl) and aseptic conditions. Both carotid arteries were exteriorized in skin loops [10] for arterial pressure recording and blood sampling. Ultrasound transit-time flow transducers were implanted around the pulmonary artery through a left-sided thoracotomy for continuous recording of cardiac output. During the convalescence the dogs were trained to lie quietly and unrestrained on their right side and to become familiar with the experimenters and the laboratory.

The following variables were recorded continuously on an eight-channel polygraph (model RS 3800®; Gould Inc., Cleveland, OH, USA) and simultaneously stored on a personal computer for further analysis after analogue-to-digital conversion with a rate of 1000 Hz (CHART®, ADInstruments, Castle Hill, Australia).

HR and respiratory rate (RR) intervals were determined from a standard electrocardiography (ECG), using surface electrodes, which triggered a rate meter providing a continuous recording of the heart periods (RR intervals).

Arterial pressure was measured electromanometrically (Statham P-23ID®; Elk Grove, IL, USA) in the ascending aorta through a catheter advanced via the carotid artery. The transducer was calibrated with a mercury manometer and referenced to the spinous process of the seventh cervical vertebra with the animals lying on the right side. Mean arterial pressure (MAP) was measured by integration of the original pressure signal. Blood pressure (BP) in the sinus of the carotid artery was measured by a second catheter that was advanced rostrally through the second exteriorized carotid artery.

Cardiac output: Blood flow through the pulmonary artery was measured continuously with an ultrasound transit-time system (T101®; Transonic Systems Inc., Ithaca, USA). Each flow transducer (20–24 mm S-series with silicone shielded U-reflector, Transonic) was calibrated in vitro prior to implantation and in vivo at least 3 weeks after implantation as previously described [11].

RR was measured continuously by a mercury-in-silastic-gauge (self-made) mounted around the animal’s thorax.

HR variability, an indicator of the activity of the autonomous nervous system, was studied as recommended [12]. The original ECG signal, free of aberrant ECG complexes and artefacts, was analysed over a period of 5 min during steady-state conditions after each incremental change in desflurane concentration (CHART®). HR variability was analysed in the frequency domain and calculated as activity in the high-frequency (HF, 0.15–0.5 Hz) and the low-frequency (LF, 0.04–0.15 Hz) range, the former showing exclusively vagal activity and the latter both vagal and sympathetic activity [12].

To assess whether potential differences in BP between groups could trigger HR changes, we measured the sensitivity of the carotid baroreflex as described previously [13]. Both carotid arteries were simultaneously occluded for 45 s with self-made external cuff occluders, resulting in a decrease in carotid sinus pressure (CSP) and an increase in HR. Carotid baroreflex sensitivity (BRS) was calculated as the quotient of changes in HR (RR intervals) and in CSP (BRS = ΔRR/ΔCSP).

During anaesthesia, respiratory gases and vapour concentrations were measured continuously at the endotracheal tube orifice by infra-red spectroscopy (Capnoma®; Ultima SV, Datex-Engström, Helsinki, Finland). We also determined intermittently arterial blood-gas tensions, O2 saturation, and pH (ABL3®; Radiometer, Copenhagen, Denmark).

All experiments were carried out with the dogs awake in basal metabolic state (food withheld for 12 h and free access to water) and under standardized conditions (lightly dimmed laboratory at thermoneutral temperature for dogs of 24°C) [14]. During the studies, which always began at 08:00 h the dogs remained unrestrained on a cushioned table. The following three experiments were performed in each animal in a randomized order. At least 1 week was allowed between successive experiments to ensure complete elimination of the administered drugs.

Control group (n = 6)
After connecting the dogs to the recording system, we waited about 30 min until all variables had reached a steady state. The actual experiments started with baseline measurements for a further 30 min with the dogs awake and breathing spontaneously. Following the insertion of an endotracheal tube (intravenous (i.v.) injection of propofol 3 mg kg⁻¹; Diprivan® 1%, Fresenius Kabi, Bad Homburg, Germany) the lungs
were ventilated with 30% of O₂ in N₂ at a constant rate of 14 breaths min⁻¹. If necessary, tidal volume was adjusted to maintain normocarbia. Desflurane (Suprane®; Baxter, Munich, Germany) was added and immediately adjusted to an end-tidal concentration of 1 MAC (7.0 volumes per cent [15]) for the duration of 30 min, and then to 2 MAC for 20 min. The exposure times were sufficiently long for the inspiratory and end-tidal concentrations of the anaesthetics to equilibrate. The exposure time of 30 min for 1 MAC was chosen to allow for the rapid redistribution phase of propofol (half-life of the α-phase of about 2 min [16]) and thus to minimize interaction with propofol.

Propranolol group (n = 6)

After baseline measurements propranolol (P 0884®, Sigma, Taufkirchen, Germany) was injected i.v. (2 mg kg⁻¹, followed by 1 mg kg⁻¹ h⁻¹ continuous infusion) to achieve sympathetic blockade. Thereafter, the same experimental program was repeated as in the control group. The completeness of receptor blockade was assessed by an i.v. injection of orciprenaline 0.5 µg kg⁻¹ at the end of the experiments. This dose increased HR by about 15 min⁻¹ and decreased arterial pressure by about 25 mmHg during pilot experiments without preceding receptor blockade and was without any detectable effect on haemodynamic variables after β-adrenergic receptor blockade, as tested in each experiment.

Atropine group (n = 6)

After baseline measurements, atropine was injected i.v. (0.1 mg kg⁻¹, followed by 0.05 mg kg⁻¹ h⁻¹) to achieve vagal blockade. Thereafter, the same experimental program as in the control group was repeated. Completeness of receptor blockade was assessed by the absence of any HR change after i.v. injection of atropine 1.0 mg at the end of each experiment.

The results of the concentration–effect relations are given as mean ± SEM. Comparisons for HR, HF, F and LF-power were made by an analysis of variance (ANOVA), followed by Fisher’s PLSD test if appropriate. P < 0.05 was considered significant. After logarithmic transformation of the results, linear correlation coefficients were calculated between HR variability (HF-power) and HR and the regression lines in the presence and absence of propranolol were compared by an F-test for differences between regression lines. P < 0.05 was considered significant.

Results

During baseline conditions (awake dogs) the HR was identical in all groups (about 60 beats min⁻¹). It was almost unchanged after propranolol (64 ± 2 beats min⁻¹) whereas atropine increased the HR to 147 ± 5 beats min⁻¹ (P < 0.0001). With the transition from the awake state to 1 MAC desflurane anaesthesia (Fig. 1), the HR increased identically in the control and propranolol-treated dogs to 107 ± 3 and 108 ± 2 beats min⁻¹, respectively (P < 0.0001 for both groups). On the contrary, in the atropine-treated dogs the HR was reduced to 120 ± 5 beats min⁻¹ (P = 0.0006). At 2 MAC of desflurane, HR increased further during control conditions to 118 ± 2 beats min⁻¹ (P = 0.0049) with no difference to the atropine group (114 ± 3 beats min⁻¹). In the propranolol dogs, HR did not increase further with the deepening of desflurane anaesthesia from 1 to 2 MAC. Yet, HR was about 12 beats min⁻¹ lower in the absence of sympathetic activity (P = 0.0066). Completeness of vagal blockade in the atropine-treated dogs can be assumed since a further dose of atropine 1 mg did not change HR (+1 ± 1 beats min⁻¹). Nor did orciprenaline 0.5 µg kg⁻¹ cause any changes in HR or arterial pressure (0 ± 1 beats min⁻¹ and −1 ± 2 mmHg) in the propranolol dogs.

The increased HR during desflurane anaesthesia in control and propranolol-treated dogs were always associated with changes in vagal activity (HF-power) in the opposite direction (Fig. 2, panel a). HF-power decreased markedly, without any difference between the two groups. In contrast, HF-power was entirely suppressed in the atropine group before the addition of desflurane, indicating successful blockade of vagal activity to the heart. LF-power decreased almost identically during desflurane in the control and
propranolol animals (Fig. 2, panel b). In the atropine dogs, LF-power was reduced in the awake state compared to control conditions and decreased further during desflurane anaesthesia.

As already indicated in Figures 1 and 2, HR correlated closely with vagal activity (HF-power) during desflurane anaesthesia, independent of the presence or absence of sympathetic activity or the anaesthetic concentration (Fig. 3). The correlation coefficients were 0.93 and 0.95 and the regression lines did not differ between the controls and the propranolol-treated dogs. In contrast, in the atropine-treated animals HR did not correlate with HF-power either in the awake state or during desflurane anaesthesia.

Additional information is summarized in Table 1. Sympathetic blockade per se did not alter any of the haemodynamic variables nor gas exchange, whereas MAP and cardiac output increased after parasympathetic blockade. During desflurane anaesthesia, particularly at 2 MAC, MAP and cardiac output were

![Heart rate variability analysed in the frequency domain (HF (a) and LF (b)) in the awake state and during desflurane anaesthesia (1 and 2 MAC) in control dogs (○ ● ●), after β-adrenoceptor blockade with propranolol (△ ●), and after parasympathetic blockade with atropine (■ ■). Values are mean ± SEM from six dogs. (a) P < 0.05 compared to 1 MAC within each group; (b) P < 0.05 compared to the control group.

Table 1. Haemodynamics, baroreflex sensitivity (BRS), and gas exchange.

<table>
<thead>
<tr>
<th>Group</th>
<th>Condition</th>
<th>MAP (mmHg)</th>
<th>Cardiac output (mL·kg⁻¹·min⁻¹)</th>
<th>PaCO₂ (kPa)</th>
<th>PaO₂ (kPa)</th>
<th>pH</th>
<th>BRS (ms·mmHg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>Awake</td>
<td>92 (2)</td>
<td>86 (7)</td>
<td>4.9 (0.1)</td>
<td>13.5 (0.6)</td>
<td>7.36 (0.01)</td>
<td>14 (4)</td>
</tr>
<tr>
<td></td>
<td>1 MAC</td>
<td>76 (3)</td>
<td>96 (6)</td>
<td>5.1 (0.1)</td>
<td>18.9 (0.3)</td>
<td>7.35 (0.01)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>2 MAC</td>
<td>63 (4)</td>
<td>79 (5)</td>
<td>5.4 (0.1)</td>
<td>16.5 (0.6)</td>
<td>7.30 (0.01)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Awake</td>
<td>91 (3)</td>
<td>86 (9)</td>
<td>5.0 (0.1)</td>
<td>13.5 (0.6)</td>
<td>7.31 (0.01)</td>
<td>13 (1)</td>
</tr>
<tr>
<td></td>
<td>Block</td>
<td>93 (3)</td>
<td>85 (11)</td>
<td>4.8 (0.1)</td>
<td>13.5 (0.6)</td>
<td>7.32 (0.01)</td>
<td>10 (2)</td>
</tr>
<tr>
<td></td>
<td>1 MAC</td>
<td>65 (1)*</td>
<td>92 (8)</td>
<td>4.8 (0.1)</td>
<td>18.9 (0.6)</td>
<td>7.30 (0.01)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>2 MAC</td>
<td>42 (3)*</td>
<td>50 (4)*</td>
<td>5.2 (0.2)</td>
<td>16.6 (0.6)</td>
<td>7.26 (0.01)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Atropine</td>
<td>Awake</td>
<td>97 (5)</td>
<td>87 (13)</td>
<td>4.8 (0.1)</td>
<td>13.1 (0.6)</td>
<td>7.29 (0.01)</td>
<td>9 (3)</td>
</tr>
<tr>
<td></td>
<td>Block</td>
<td>109 (5)*</td>
<td>108 (12)*</td>
<td>4.8 (0.2)</td>
<td>14.4 (0.7)</td>
<td>7.32 (0.01)</td>
<td>1 (0)</td>
</tr>
<tr>
<td></td>
<td>1 MAC</td>
<td>79 (8)</td>
<td>92 (11)</td>
<td>5.2 (0.2)</td>
<td>16.3 (1.5)</td>
<td>7.28 (0.01)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>2 MAC</td>
<td>57 (2)*</td>
<td>66 (7)*</td>
<td>4.9 (0.2)</td>
<td>16.1 (0.8)</td>
<td>7.27 (0.01)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

MAP: mean arterial pressure. Values are mean (SEM) for six dogs. *P < 0.05 vs. control experiments; †P < 0.05 vs. the propranolol group.
lower in the propranolol-treated dogs. Carotid baroreflex sensitivity did not differ between groups in the awake state and during anaesthesia with desflurane. Carotid baroreflex sensitivity was zero during desflurane anaesthesia at 1 and 2 MAC in all groups, indicating that decreases in CSP are not compensated for by changes in HR. The respiratory rate was similar at baseline in all awake dogs, and during anaesthesia respiratory rate was kept constant throughout the experiments.

Discussion

We have shown that desflurane elicits tachycardia with a corresponding decrease in HR variability, both in the presence and absence of sympathetic activity. Parasympathetic blockade per se increased HR with no further increase in the presence of desflurane. Thus, HR changes during desflurane anaesthesia are independent of the sympathetic nervous system and most probably result from vagal inhibition.

Our conclusions imply that a sufficient degree of blockade of sympathetic and parasympathetic activity had been achieved. We also make the tenable assumption that HR variability is a measure of autonomic activity, particular vagal activity.

Sympathetic activity was blocked by propranolol in a dose of 2 mg kg\(^{-1}\) initially, followed by 1 mg kg\(^{-1}\) h\(^{-1}\). This \(\beta\)-adrenoceptor antagonist blocks both \(\beta_1\)- and \(\beta_2\)-receptors and has no agonistic effects on these receptors [17]. The chosen dosage is comparable to that used by others to block sympathetic activity in dogs [18]. The completeness of \(\beta\)-adrenoceptor blockade in our experiments was verified by the administration of a \(\alpha\)-agonist (orcinoprenaline 0.5 \(\mu\)g kg\(^{-1}\)), which did not cause any changes in HR or arterial pressure. This dose has been shown previously in pilot studies to cause an increase in HR of about 15 beats min\(^{-1}\) and a decrease in arterial pressure of about 25 mmHg in animals without preceding \(\beta\)-adrenoceptor blockade.

Vagal activity to the heart was blocked by atropine 0.1 mg kg\(^{-1}\), followed by 0.05 mg kg\(^{-1}\) h\(^{-1}\). Completeness of receptor blockade can be assumed from two observations: First, in pilot experiments a further dosage increase did not change HR in these dogs. Moreover, 1 mg atropine given at the end of each experiment in this study did not induce any change in HR.

Autonomic activity is the spike traffic in sympathetic neurons and cardio-inhibitory vagal neurons. Direct recording from these nerves cannot be made in the intact organism, in particular if repetitive experiments in one and the same animal are performed. However, as a surrogate for direct nerve recordings, beat-to-beat changes in HR, termed HR variability, are used as indices of autonomic activity. Spectral analysis of instantaneous HR (analysis in the frequency domain) in a frequency range coincident with respiration (respiratory frequency 0.15–0.5 Hz, HF) is believed to exclusively reflect vagal activity [12]. HR also changes with fluctuation in arterial pressure (frequency band 0.04–0.15 Hz, LF), which was believed to reflect sympathetic activity only, but has been shown to contain both sympathetic and vagal activity [12,19,20]. This view is supported by our own experiments in which LF-power was reduced by the parasympathetic blockade indicating that the information included in LF-power does not consist of only sympathetic activity.

HR variability may be influenced by changes in PaCO\(_2\), respiratory rate, and tidal volume [21,22]. Since the influence of tidal volume is small compared to that of respiratory rate [21,22], the animals were ventilated at the same rate and only tidal volume was varied (up to 20%) to maintain normocarbia. Accordingly, our methods were able to detect differences in the HR changes during desflurane anaesthesia related to the presence and absence of sympathetic and vagal activity, respectively.

HR increases during desflurane anaesthesia have been observed in man [3] as well as in dogs [2,6]. In parallel to HR, desflurane increases sympathetic activity, which has been shown particularly for fibres supplying peripheral muscles [3]. These effects are more pronounced during transient increases in desflurane concentrations compared to steady-state conditions [23]. The transient component of the HR increase at desflurane concentrations of about 1 MAC seems to be influenced by the sympathetic nervous system as evidenced by the fact that \(\beta\)-adrenoceptor blockade attenuates this response [23]. In addition, direct recordings from renal nerves in dogs have revealed that sympathetic activity was increased only at desflurane concentrations up to 1 MAC, whereas it was strongly reduced at concentrations above 1 MAC [6]. These results are not in accordance with our own, since we found a strong reduction in LF-power at 1 MAC, although LF-power tended to be higher in the control experiments compared to the \(\beta\)-adrenoceptor blocked group. However, these differences in LF-power are obviously of only minor importance for HR adjustment during desflurane anaesthesia, since HR was identical in both controls and propranolol-treated dogs at 1 MAC. Moreover, HR correlated closely with all measures of autonomic activity and the regression lines did not differ between animals with or without \(\beta\)-blockade at either 1 or 2 MAC (Fig. 3). Since sympathetic inhibition, as indicated by the marked reduction in LF-power, cannot explain tachycardia, vagal inhibition remains the only rationale for the HR increase during desflurane anaesthesia. This is also

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supported by the fact that HR did not increase in dogs pre-treated with atropine, i.e. in the absence of vagal activity. In fact HR rather decreased at 1 MAC in these dogs which can only be explained by suppression of the remaining sympathetic activity.

At 2 MAC of desflurane, HR did not differ between controls and dogs given atropine. HR was slightly lower in the β-blocked dogs, i.e. in the absence of sympathetic activity. One might speculate that this difference results from sympathetic activation, which is most unlikely, since direct nerve recordings uniformly have yielded strongly suppressed sympathetic activity at this concentration [6] and LF-power in our own experiments did not differ between groups. Accordingly, the difference in HR at 2 MAC of desflurane probably does not result from sympathetic activation, although we have no tenable alternative explanation. It is obvious that cardiac output and BP were lower in the absence of sympathetic activity (β-blocked dogs) compared to desflurane alone only at 2 MAC of desflurane. With due caution, we may speculate that cardiac vagal afferents located in the ventricles could be activated during conditions with compromised circulation leading to an additional slowing of HR [24]. This phenomenon has been observed during bleeding experiments, in which HR decreased in parallel to further reductions in arterial pressure once the pressure fell below a certain level [25,26].

Desflurane has previously been shown to release intramyocardial catecholamines in vitro [7]. However, like all other inhalational agents desflurane decreases HR in a concentration-dependent fashion in isolated hearts [9] and it has not been shown to change systemic plasma catecholamine concentrations [8]. Thus, during desflurane anaesthesia in vivo, intramyocardial catecholamine release should only make a minor contribution to the HR adjustment. It is also unlikely that baroreflex activation triggers tachycardia, since desflurane like all other volatile anaesthetics suppresses the baroreflex sensitivity [27,28] and this was already substantially reduced at 1 MAC in our own experiments.

Our study suggests, that although sympathetic activation of the muscles and the kidneys has been observed during desflurane anaesthesia, the increase in HR most probably has a different explanation. We found similar degrees of tachycardia during desflurane anaesthesia in dogs in the presence or absence of β-adrenoceptor blockade making a substantial contribution of the sympathetic nervous system unlikely. In contrast, once vagal activity to the heart was blocked with atropine, desflurane did no longer increase HR. Thus, HR adjustment during desflurane anaesthesia seems to result from vagal inhibition which is in accordance with other inhalation anaesthetics [2]. From a clinical point of view, there is no reason to avoid desflurane in patients in whom sympathetic activation to the heart is undesirable.

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References


