Inhalation anaesthetics increase heart rate by decreasing cardiac vagal activity in dogs

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Inhalation anaesthetics decrease heart rate in isolated hearts but mostly increase heart rate in the intact organism, although most inhibit sympathetic drive. Differences in the degree of increase in heart rate between agents may be related to differences in their vagolytic action. To test this hypothesis, we studied the effects of halothane (H), isoflurane (I), enflurane (E), sevoflurane (S) and desflurane (D) [1–3 MAC (minimum alveolar concentration)] on heart rate and heart rate variability (HRV) as a measure of cardiac vagal activity in seven dogs. HRV was analysed in the time domain as the standard deviation of the RR interval (SDNN) and in the frequency domain as power in the high-frequency (HF, 0.15–0.5 Hz) and low-frequency (LF, 0.04–0.15 Hz) ranges. Heart rate increased with anaesthetic concentration and there were corresponding decreases in SDNN, HF power and LF power. Heart rate increased most with D (+40 beats min⁻¹), least with H (+8 beats min⁻¹) and to an intermediate extent with S, I and E. SDNN and HF power, as measures of vagal activity, changed in the opposite direction and decreased in the same order as heart rate increased. However, SDNN and HF power correlated significantly with heart rate [r=−0.81 (0.04) and −0.81 (0.03) respectively] and were independent of the anaesthetic and its concentration (P<0.05). Consistent with our hypothesis, these results suggest that differences between agents in the degree of increase in heart rate are explained by differences in their vagolytic action.

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Inhalation anaesthetics increase heart rate (HR) in vivo both in animals¹–³ and humans,⁴⁻⁵ but decrease heart rate in isolated hearts.⁶⁻⁷ In the intact organism, HR increases with increasing anaesthetic concentration, i.e. with the depth of anaesthesia but, curiously and for unknown reasons, HR increases more with the halogenated ethers, in particular desflurane, than with the strained-chain hydrogencarbon halothane.³⁻⁴⁻⁸⁻⁹ Activation of the sympathetic nervous system may explain the increase in HR during desflurane or isoflurane anaesthesia, which has been shown to be associated with increases in spike traffic in sympathetic nerves innervating skeletal muscle in humans.⁸⁻¹⁰ This effect, however, is more pronounced during transient than during steady-state conditions.¹⁰ For the other inhalation anaesthetics, this explanation is at variance with the large body of evidence showing inhibition rather than activation of sympathetic drive,¹¹ particularly at deeper levels of anaesthesia.¹²

Under physiological conditions, HR is determined primarily by cardiac vagal activity,¹³ but surprisingly little is known about its response to anaesthesia. Halothane decreases spike traffic in efferent cardiac vagal nerves,¹⁴ but corresponding information is lacking for other inhalation anaesthetics. By the use of HR variability (HRV) as an indicator of cardiac vagal activity, vagal inhibition has also been shown for halothane anaesthesia in dogs and for isoflurane anaesthesia in humans.¹⁵⁻¹⁶ This fragmentary information suggests that cardiac vagal activity may also determine HR during inhalation anaesthesia and that differences between agents in the degree of increase in HR may reflect differences in their vagolytic action. We tested
this hypothesis in dogs by looking at the effects of five currently used inhalation anaesthetics [1–3 MAC (minimum alveolar concentration)] on HR and HRV as an indicator of cardiac vagal activity.

Methods
The data derive from seven trained dogs (Foxhounds of both sexes, weighing 24–34 kg) studied with approval of the District Governmental Animal Investigation Committee. Each dog received, in random order, each of five anaesthetics [halothane (H), enflurane (E), isoflurane (I), desflurane (D) and sevoflurane (S)], with an interval of at least 1 week between successive experiments in the same animal, so that each dog served as its own control.

Several weeks before the experiments, the dogs were operated under general anaesthesia (enflurane/nitrous oxide+fentanyl) and aseptic conditions. For arterial blood pressure recording and blood sampling, both carotid arteries were exteriorized in skin loops.17 Ultrasound transit-time flow transducers were implanted around the pulmonary artery through a left-sided thoracotomy for the continuous recording of cardiac output. 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.

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 1000 Hz.

Heart rate and RR interval
HR and RR interval (heart period) were determined from a standard ECG (surface electrodes) that was used for triggering a rate meter, which provided a continuous recording of the RR interval.

Arterial blood pressure
Arterial blood pressure was measured electromanometrically (Statham P-23ID, Elk Grove, USA) through a catheter in the carotid artery. The electromanometer was calibrated with a mercury manometer and referenced to the processus spinosus of the 7th vertebra while the animals were lying on their right side. Mean arterial pressure was measured by integrating the original pressure signal.

Cardiac output
Blood flow through the pulmonary artery was measured continuously with an ultrasound transit-time system (T101; Transonic Systems, Ithaca, NY, USA). Each flow transducer (20–24 mm S-series with silicone-shielded U-reflector; Transonic Systems) was calibrated in vitro before implantation and in vivo at least 3 weeks after implantation by the Fick principle from oxygen consumption (V\textsubscript{O\textsubscript{2}}), measured by indirect calorimetry (Deltatrac II\textsuperscript{18}), and the arterial—mixed venous oxygen content difference (C(a–v)\textsubscript{O\textsubscript{2}}), measured with a galvanic cell (Lex-O\textsubscript{2}-Con-TL, Lexington Instruments, Waltham, USA), giving high precision, as described previously.18

Respiratory rate
Respiratory rate was measured continuously with a mercury-in-Silastic gauge mounted around the animal’s thorax.

Heart rate variability
HRV, an indicator of the activity of the autonomous nervous system, was studied as described.19 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 concentration of the respective inhalation anaesthetic (CHART; ADInstruments, Castle Hill, Australia). HRV was analysed in the time domain and expressed as the standard deviation of the RR interval (SDNN). In addition, HRV was analysed in the frequency domain and calculated as the activity in the high-frequency (HF, 0.15–0.5 Hz) and the low-frequency (LF, 0.04–0.15 Hz) ranges, the former showing exclusively vagal activity and the latter both vagal and sympathetic activity.

During anaesthesia, respiratory gases and vapour concentrations were measured continuously at the endotracheal tube orifice by infrared spectroscopy (Capnomac; Ultima, Datex-Engstrom, Finland). We also intermittently determined arterial blood gas tensions, oxygen saturation and pH (ABL3; Radiometer, Copenhagen, Denmark).

All experiments were carried out with awake dogs in the basal metabolic state (food was withheld for 12 h with free access to water) and under standardized experimental conditions [slightly dimmed laboratory lighting; thermo-neutral temperature for dogs (24°C)].20 During the experiments, which always began at 8 a.m., the dogs remained unrestrained on a cushioned table. To ensure complete elimination of the inhalation anaesthetics, there was an interval of at least 1 week between successive experiments.

After connecting the animals to the recording system, a 30 min stabilization period was commenced. Each experiment began with baseline measurements occupying 30 min, while the awake animals breathed spontaneously. After the insertion of an endotracheal tube (intravenous injection of propofol 3 mg kg\textsuperscript{−1}), the animals’ lungs were ventilated with air at a constant rate and, if necessary, tidal volume was adjusted to maintain normocarbia. In the case of desflurane, the vapour was fed together with oxygen-enriched air (30% oxygen in nitrogen) to prevent hypoxia. The anaesthetics were added and immediately adjusted to an end-tidal concentration of 1 MAC (30 min for 1 MAC to minimize
interaction with propofol) and then to 2 and eventually to 3 MAC (for 20 min). Exposure times were sufficient for the inspiratory and end-tidal concentrations of the anaesthetics to equilibrate.

In addition, we repeated the experiments with D in the presence of β-receptor blockade (propranolol 2 mg kg⁻¹ initially, followed by 1 mg kg⁻¹ h⁻¹) in two dogs, to exclude the contribution of the sympathetic nervous system to the effects of D on heart rate.

In agreement with the literature, MAC values were assumed to be 0.8, 1.6, 1.4, 2.0 and 7.0 vol% for halothane, enflurane, isoflurane, sevoflurane and desflurane respectively, and the anaesthetics were delivered with conventional vaporizers (Dräger, Lübeck, Germany). Because of limitations of the vaporizers, anaesthetic concentrations had to be restricted to 2.5 and 2.0 MAC for sevoflurane and desflurane respectively.

Results for concentration–effect relationships are given as mean (SEM). Comparisons for heart rate, SDNN and HF and LF power were made by analysis of variance for repeated measures with anaesthetic as between factor. Individual comparisons were made by Fisher’s PLSD if appropriate. P < 0.05 was considered statistically significant.

After logarithmic transformation of the results, linear correlation coefficients were calculated between HRV (SDNN, HF and LF power) and HR for all experiments in one dog and the following null hypothesis was tested: HR during inhalation anaesthesia is independent of vagal activity (SDNN and HF power). For this purpose, the individual correlation coefficients were calculated and compared using a sign test. The null hypothesis was rejected and statistical significance assumed when P < 0.05.

Results

In general, HR increased and was associated with a decrease in HRV during inhalation anaesthesia. These effects

![Graph 1](image1.png)

**Fig 1** Heart rate (A) and heart rate variability (B) analysed in the time domain (SDNN) during baseline conditions (awake, open symbols) and during anaesthesia with increasing concentrations of five inhalation anaesthetics (closed symbols). Values are mean and SEM for seven dogs. Heart rate increased and SDNN decreased with increasing anaesthetic concentration (P < 0.05); *indicates differences between the anaesthetics.

![Graph 2](image2.png)

**Fig 2** Heart rate variability analysed in the frequency domain [HF (A) and LF (B)] during baseline conditions (awake, open symbols) and during anaesthesia with increasing concentrations of five inhalation anaesthetics (closed symbols). Values are mean and SEM for seven dogs. HF and LF power decreased with the anaesthetic concentration (P < 0.05) with differences between the anaesthetics. *HF and LF power decreased most during increasing concentrations of sevoflurane and desflurane, and least during halothane anaesthesia.
increased with the concentration of anaesthetic but differed markedly between agents. This is shown by the concentration–effect relationships in Figure 1. At baseline (awake, basal metabolic state), the animals always had a low HR (73–77 beat min⁻¹) with strong HRV (193–230 ms), showing the presence of substantial vagal activity before induction of anaesthesia in all groups. During anaesthesia, HR increased with increasing anaesthetic concentration (P<0.05) but, at each MAC, HR changed most with D, less with S, I and E, and least with H. Differences in the degree of increase in HR were substantial; for instance, at 2 MAC the HR was only 73 (4) beats min⁻¹ in the presence of H but 117 (2) beats min⁻¹ in the presence of D and between the two extremes for the other agents.

These HR changes were always associated with changes in HRV in the opposite direction (Fig. 1B). HRV was already substantially reduced, by about 80%, with the loss of consciousness (i.e. on the transition from awake to 1 MAC), and decreased further to a fraction of the baseline value at ≥2 MAC (P<0.05). Note in particular that, at 2 MAC, HRV reached a minimum in the presence of D and S while HRV was about 10 times greater in the presence of H. Thus, the analysis of HRV in the time domain, which mainly reflects cardiac vagal activity, indicates a vagolytic effect and corresponding opposite changes in HR. These effects differed between agents as they were least for H, greatest for D and S and intermediate for E and I.

Similar results were obtained by more detailed analysis of HRV in the frequency domain (Fig. 2). At baseline, HF power was about 10 times greater than LF power, reflecting the predominance of vagal activity in the awake state. During anaesthesia, both indices of the activity of the autonomic nervous system decreased as MAC increased (P<0.05); this effect was least for H, greatest for D and S, and intermediate for E and I. Note also the magnitude of these effects: both HF and LF power decreased by about 99% and reached a minimum at 2 MAC for both S and D.

Thus, analysis of HRV showed that the five inhalation anaesthetics inhibited vagal activity in a concentration-related manner. However, these effects differed between agents as at ≥2 MAC vagal activity was strongly reduced in the presence of D and S, less so for E and I, and least for H.

Regardless of these substance-specific differences, HR correlated significantly with the indices of vagal activity during inhalation anaesthesia, independently of the anaesthetic or its concentration (Fig. 3). The correlation coefficients for all experiments in each animal were mostly <0.8 (see inset in Fig. 3). Thus, vagal activity probably determines and regulates HR during inhalation anaesthesia and, accordingly, the substance-specific differences in the degree of increase in HR are related to the level of vagal activity. This interpretation also applies to D, which increased HR even after β-receptor blockade in two dogs from 62 and 74 beats min⁻¹ to 114 and 107 beats min⁻¹ at 2 MAC in parallel to a reduction in HF power and SDNN by about 99%.

To help in the interpretation of our observations, additional information is summarized in Table 1. Mean arterial blood pressure and cardiac output decreased substantially as MAC increased but there were no differences between anaesthetics. Respiratory rate was essentially the same during baseline in awake animals, and during anaesthesia respiratory rate was maintained for each animal throughout the experiment.

**Discussion**

We have shown that inhalation anaesthetics elicit a concentration-related increase in HR with a corresponding
decrease in HRV, but, at equi-anesthetic concentrations, these effects differ substantially between agents.

Our conclusions rest primarily on the tenable premise that HRV is a measure of cardiac vagal activity. By definition, cardiac vagal activity is the spike traffic in cardioinhibitory vagal neurones which to date cannot be recorded in the intact organism. As a rule, vagal spike frequency correlates linearly with HR, which, in turn, correlates linearly with the respiratory changes in HR, i.e. the degree of respiratory arrhythmia.\(^2\)\(^4\) The correspondence of these correlations is the rationale for using respiratory changes in HR, expressed as standard deviations, for instance as an index of cardiac vagal activity. This information can be derived simply from continuous recording of beat-to-beat HR (analysis in the time domain). Apart from the vagally mediated HR changes coincident with respiration (respiratory frequency 0.15–0.5 Hz), HR also changes with fluctuations in arterial blood pressure (frequency band 0.05–0.15 Hz), which are associated with changes in sympathetic activity. These two components can be separated by spectral analysis of instantaneous HR (analysis in the frequency domain), and there is agreement that power in the HF band reflects exclusively vagal activity. Power in the LF band, which was primarily thought to reflect only sympathetic activity, has been shown to contain both sympathetic and vagal activity.\(^1\)\(^9\)\(^2\)\(^5\)\(^2\)\(^6\) Despite these uncertainties, we have included the analysis of the LF range for completeness.

HRV may be influenced by changes in \(\text{PCO}_2\), respiratory rate and tidal volume.\(^2\)\(^7\)\(^2\)\(^8\) Because the influence of tidal volume is small compared with that of respiratory rate,\(^2\)\(^7\)\(^2\)\(^8\) the animals were ventilated at the same rate and only tidal volume was varied to maintain normocarbia. Moreover, HRV is strongly reduced by the transition from the awake state (with spontaneous respiration) to anaesthesia (with controlled ventilation).\(^2\)\(^9\) To avoid such interference, we tested only the results obtained during anaesthesia with controlled ventilation. Thus, HRV at respiratory frequencies (activity in the HF range) is a reliable indicator of cardiac vagal activity in our experiments.

The degree of increase in HR differed substantially between the five inhalation anaesthetics. At equi-anesthetic concentrations, the increase was greatest for D (40 beats min\(^{-1}\)), least for H (8 beats min\(^{-1}\)) and intermediate for S, I and E. This essentially confirms previous observations in dogs\(^1\)\(^–\)\(^3\) and humans,\(^5\) although the results in humans seem to be less clear at lower concentrations of inhalation anaesthetics.\(^8\)\(^\,\)\(^1\)\(^0\) Nevertheless, our experiments show for the first time corresponding differences in the strength of vagolytic activity of inhalation anaesthetics.

In contrast to in vivo experiments, studies with inhalation anaesthetics uniformly show decreased HR in isolated hearts or isolated pacemaker cells. In vivo, they also inhibit sympathetic activity, which would promote decreases—certainly not increases—in HR. At first glance, D seems to be exceptional because it activates specifically sympathetic fibres supplying peripheral blood vessels more during transient conditions than during steady-state conditions.\(^1\)\(^0\) Nevertheless, D evoked greater changes in HR than isoflurane, whereas norepinephrine concentrations did not differ between agents,\(^2\)\(^0\) so that D is not a general stimulant of the sympathetic nervous system. Moreover, although D

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Table 1 Haemodynamic variables and gas exchange. MAP=mean arterial pressure. Values are mean (SEM) for seven dogs

<table>
<thead>
<tr>
<th>Agent</th>
<th>MAC (mmHg)</th>
<th>MAP (mmHg)</th>
<th>Cardiac output (ml kg(^{-1}) min(^{-1}))</th>
<th>Respiratory rate (min(^{-1}))</th>
<th>(\text{PCO}_2) (mmHg)</th>
<th>(\text{PO}_2) (mmHg)</th>
<th>pH</th>
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<tr>
<td>Isoflurane</td>
<td>0</td>
<td>94 (3)</td>
<td>108 (6)</td>
<td>21 (2)</td>
<td>33 (1)</td>
<td>98 (2)</td>
<td>7.39 (0.01)</td>
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<tr>
<td></td>
<td>1</td>
<td>67 (3)</td>
<td>86 (8)</td>
<td>14 (1)</td>
<td>34 (1)</td>
<td>104 (3)</td>
<td>7.38 (0.01)</td>
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<td></td>
<td>2</td>
<td>46 (3)</td>
<td>64 (8)</td>
<td>14 (1)</td>
<td>34 (1)</td>
<td>104 (4)</td>
<td>7.37 (0.02)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>33 (1)</td>
<td>40 (4)</td>
<td>14 (1)</td>
<td>33 (1)</td>
<td>106 (6)</td>
<td>7.38 (0.01)</td>
</tr>
<tr>
<td>Desflurane</td>
<td>0</td>
<td>93 (2)</td>
<td>194 (5)</td>
<td>23 (2)</td>
<td>35 (1)</td>
<td>103 (4)</td>
<td>7.38 (0.01)</td>
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<tr>
<td></td>
<td>1</td>
<td>72 (3)</td>
<td>81 (5)</td>
<td>13 (1)</td>
<td>34 (1)</td>
<td>147 (7)</td>
<td>7.37 (0.02)</td>
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<td>58 (7)</td>
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<td>34 (1)</td>
<td>92 (3)</td>
<td>7.41 (0.01)</td>
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<tr>
<td>Halothane</td>
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<td>101 (5)</td>
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<td>107 (4)</td>
<td>7.40 (0.01)</td>
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<td>105 (5)</td>
<td>7.38 (0.01)</td>
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Picker et al. 752
has been shown to release intramyocardial catecholamines,\textsuperscript{31} this agent, like the others, decreased HR in a

dose-dependent fashion in isolated hearts.\textsuperscript{32} In additional

experiments we showed that D produced the same
tachycardia even after β-receptor blockade.

Accordingly, during inhalation anaesthesia, cardiac vagal

activity is the remainder of the autonomous nervous system

participating in the central control of HR. That inhalation

anaesthetics inhibit cardiac vagal activity has been shown

before for two agents. For instance, halothane decreased

both spike traffic in cardioinhibitory neurones\textsuperscript{14} and HRV in
dogs,\textsuperscript{36} as isoflurane does in humans.\textsuperscript{15} Our experiments

revealed agent-specific differences in the strength of

vagolytic action. Regardless of the agent used, the indices

of cardiac vagal activity (HRV and HF power) decreased in

a dose-related manner, i.e. with the depth of anaesthesia, but

the magnitude of this effect increased in the same order as

HR increased. At 2 MAC, the indices of cardiac vagal

activity decreased to a fraction of the baseline value and had

reached a minimum in the presence of either D or S. Vagal

activity was still 10 times greater in the presence of H. The

corresponding HR was approximately 70 beats min\(^{-1}\) in the

case of H but nearly 120 beats min\(^{-1}\) in the case of D. This is

the HR that is seen after complete blockade of cardiac vagal

activity either by atropine or by cutting the vagal nerves in

both dogs and humans.\textsuperscript{33 34} The agreement between the

drug-specific changes in both HR and the indices of cardiac

vagal activity and the close correlation between the two

variables (Fig. 3) suggest that, during inhalation anaesthesia,

HR depends primarily on cardiac vagal activity. This

interpretation is justified because the positive chronotrophic

effects of the inhalation anaesthetics are unlikely to have

been evoked by the accompanying inhibition of sympathetic

drive or direct effects on the heart’s pacemaker cells.\textsuperscript{6 7 35}

Thus, our observations support the hypothesis that the
differences between inhalation anaesthetics in the degree of

increase in HR result from differences in their vagolytic

action.

Of note, cardiac output, which has been shown to depend

primarily on \(\dot{V}_O\) during inhalation anaesthesia,\textsuperscript{36} decreased

uniformly in spite of vagally mediated increases in HR.

We cannot explain why, at the same level of anaesthesia,
some anaesthetics inhibit the autonomic nervous system

more than others. Anaesthetics at high concentrations may

stimulate irritant receptors of the airways,\textsuperscript{4 37} although the

spike traffic from these receptors decreased in a dose-related

manner—to the greatest extent for sevoflurane,\textsuperscript{38} which is

generally accepted as a non-pungent and non-irritating

anaesthetic. Accordingly, stimulation of irritant receptors

can explain only the transient tachycardia during the

induction phase of desflurane anaesthesia, not the continu-

ous increase in HR that occurs at deeper levels of

anaesthesia, which are known to suppress any cardiovas-

cular response to manipulation of the airways. It is also

unlikely that differences in baroreflex activity would

account for the differences in HR between the various

inhalation anaesthetics. All suppress baroreflex activity to a

similar extent\textsuperscript{39–42} and decreased arterial blood pressure to a

similar extent in our own experiments.

One limitation of this study is that the autonomic balance

in dogs differs from that observed in humans. Whereas

vagal activity predominates in the control of HR in dogs, as

also shown in this study, the sympathetic nervous system

makes a larger contribution than vagal activity in humans.\textsuperscript{19}

But regardless of these differences, the principle responses

of the autonomous nervous system do not differ between the

two species. Accordingly, although autonomic balance is

not identical in humans and dogs, our conclusions should,

with caution, also apply to humans.

HRV reflects the activity of cardioinhibitory neurones in

the brainstem. These neurones constitute the final common

pathway for all vagally mediated HR changes, not only

those of reflex origin via irritant receptors or baroreceptors,

for instance, but also those of cortical origin, and hence the

state of awareness. It is also of interest that inhalation

anaesthetics decrease somatosensory function uniformly,

but at the same concentration inhibit the activity of the

autonomic nervous system in an agent-specific manner.

Regardless of these general considerations, our experi-

mental findings are consistent with the hypothesis that the

differences in the degree of increase in HR between five

inhalation anaesthetics are explained by differences in their

vagolytic action.

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