Xenon increases total body oxygen consumption during isoflurane anaesthesia in dogs

O. Picker1*, A. W. Schindler1, L. A. Schwarte1, B. Preckel1, W. Schlack1, T. W. L. Scheeren1 and V. Thämer2

Departments of 1Anaesthesiology and 2Physiology, Heinrich-Heine-University, Moorenstrasse 5, D-40225 Düsseldorf, Germany
*Corresponding author

Background. This study was designed to examine whether the coupling between oxygen consumption (\(V_O2\)) and cardiac output (CO) is maintained during xenon anaesthesia.

Methods. We studied the relationship between \(V_O2\) (indirect calorimetry) and CO (ultrasound flowmetry) by adding xenon to isoflurane anaesthesia in five chronically instrumented dogs. Different mixtures of xenon (70% and 50%) and isoflurane (0–1.4%) were compared with isoflurane alone (1.4% and 2.8%). In addition, the autonomic nervous system was blocked (using hexamethonium) to study its influence on \(V_O2\) and CO during xenon anaesthesia.

Results. Mean (SEM) \(V_O2\) increased from 3.4 (0.1) ml kg\(^{-1}\) min\(^{-1}\) during 1.4% isoflurane to 3.7 (0.2) and 4.0 (0.1) ml kg\(^{-1}\) min\(^{-1}\) after addition of 70% and 50% xenon, respectively (P<0.05), whereas CO and arterial pressure remained essentially unchanged. In contrast, 2.8% isoflurane reduced both, \(V_O2\) [from 3.4 (0.1) to 3.1 (0.1) ml kg\(^{-1}\) min\(^{-1}\)] and CO [from 96 (5) to 70 (3) ml kg\(^{-1}\) min\(^{-1}\)] (P<0.05). \(V_O2\) and CO correlated closely during isoflurane anaesthesia alone and also in the presence of xenon (\(r^2\)=0.94 and 0.97, respectively), but the regression lines relating CO to \(V_O2\) differed significantly between conditions, with the line in the presence of xenon showing a 0.3–0.6 ml kg\(^{-1}\) min\(^{-1}\) greater \(V_O2\) for any given CO. Following ganglionic blockade, 50% and 70% xenon elicited a similar increase in \(V_O2\), while CO and blood pressure were unchanged.

Conclusions. Metabolic regulation of blood flow is maintained during xenon anaesthesia, but cardiovascular stability is accompanied by increased \(V_O2\). The increase in \(V_O2\) is independent of the autonomic nervous system and is probably caused by direct stimulation of the cellular metabolic rate.

Br J Anaesth 2002; 88: 546–54

Keywords: anaesthetic techniques, inhalation; anaesthetics gases, xenon; heart, cardiac output; metabolism, oxygen consumption

Accepted for publication: November 11, 2001

Metabolic regulation contributes to the adjustment of the circulation in order to meet tissue oxygen demand, and manifests itself as a linear relationship between blood flow (i.e. cardiac output [CO]), and oxygen consumption (\(V_O2\)) during physiological conditions (e.g. physical exercise) in dogs and humans. We have recently shown that this fundamental principle is preserved during inhalation anaesthesia with the five volatile anaesthetics currently in use, unless the anaesthetic concentration exceeded 2 MAC. This finding implies that increasing anaesthetic depth reduces \(V_O2\) and CO in parallel. We have also shown that the decrease in CO during inhalation anaesthesia is mainly a consequence of reduced metabolic rate rather than a direct side-effect of the anaesthetic.

Recently, the noble gas xenon has been the subject of widespread interest because it has minimal effects on the cardiovascular system, leading to haemodynamic stability. This cardiovascular stability has been explained by the fact that xenon does not alter myocardial function in humans and animals or in isolated hearts. This haemodynamic stability with an unchanged CO despite an increase in anaesthetic depth is in contrast to findings with other volatile anaesthetics, which reduce \(V_O2\) and CO in parallel.
Xenon and oxygen consumption

We therefore questioned whether, and to what extent, xenon alters $V_{\text{O}_2}$ and whether metabolic regulation of blood flow is maintained during xenon anaesthesia. To test this, we studied the relationship between CO and $V_{\text{O}_2}$ during different levels of xenon anaesthesia added to an isoflurane baseline in chronically instrumented dogs and compared the effects of xenon with those elicited by isoflurane.

Methods

The data derive from 15 experiments on five trained dogs (foxhounds of both sexes weighing 24–34 kg) studied with the approval of the District Governmental Animal Investigation Committee. Each dog was assigned to each of the three intervention groups with an interval of at least 1 week between successive experiments in the same animal, so that each dog served as its own control.

Surgery

Several weeks before the experiments, the dogs were operated on under general anaesthesia (enflurane/nitrous oxide + fentanyl) and aseptic conditions. For blood pressure recording and blood sampling, both carotid arteries were exteriorized in skin loops.8 Ultrasound transit-time flow transducers were implanted around the pulmonary artery through a left-sided thoracotomy for continuous recording of CO.

Measurements

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-reflectors; Transonic Systems) was calibrated in vitro before implantation and in vivo at least 3 weeks after implantation, using the Fick principle from $\text{V}_{\text{O}_2}$ and the arterial-to-mixed venous oxygen content difference (C(a-v)$\text{O}_2$) measured with a galvanic cell (Lex-O2-Con-TL, Lexington Instruments, Waltham, USA), resulting in high precision, as described previously.9

Oxygen uptake ($V_{\text{O}_2}$)

$V_{\text{O}_2}$ (at standard temperature [273 K], pressure [760 mmHg] and dry $P_{\text{H}_2\text{O}}$ 0 mm Hg]) was measured continuously by indirect calorimetry with a Deltatrac II metabolic monitor (Datex-Engstrom Division, Instrumentarium Corp., Helsinki, Finland). Before each experiment, the gas sensors were calibrated with air and a gas mixture containing 95.0 (0.05)% $\text{O}_2$ and 5.0 (0.03)% $\text{CO}_2$, and the measurement of $V_{\text{O}_2}$ was calibrated by burning 5 ml pure ethanol (alcohol burning test kit, Datex-Engstrom, Helsinki, Finland).

Burning of alcohol was also repeated in the presence of 50 and 70% xenon to ensure that the high density of xenon did not alter the flow constant of the built-in flow generator. In addition, baseline stability of the gas sensors was tested by feeding xenon to the mixing chamber of the Deltatrac II to check if xenon alters $\text{O}_2$ and $\text{CO}_2$ measurements.

During spontaneous breathing in awake dogs, $V_{\text{O}_2}$ was measured with a flow-through technique (canopy mode), as described previously,10 which calculated $V_{\text{O}_2}$ from the difference of inspired and expired oxygen concentration and the constant gas flow through the built-in flow generator. For this purpose, a transparent plastic canopy was fixed above the dog’s head and upper trunk, allowing room air to enter at the edges as air was sucked continuously through the Deltatrac II for analysis. A canopy volume of approximately 70 litres and a flow generator rate of about 40 litre min$^{-1}$ resulted in a system time constant of 1.75 min.

During anaesthesia and controlled ventilation $V_{\text{O}_2}$ was measured directly from the respiratory gases. The expired air was collected and fed to the mixing chamber of the Deltatrac II (respiration mode, a collection technique with a time constant of 1 min). As a cross-check of the Deltatrac II measurements, we also intermittently measured $V_{\text{O}_2}$ from the product of CO and C(a-v)$\text{O}_2$ (pulmonary artery catheter). In agreement with others,11 12 the precision of this device was 3.5% (average coefficient of variation) and the accuracy was 0.1 ml min$^{-1}$, with 95% confidence intervals of 4.8 to 5.0 ml min$^{-1}$.

Arterial pressure

Arterial 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 dogs were lying on its right side. Mean arterial pressure (MAP) was measured by integration from the original pressure signal.

Heart rate and RR intervals

HR and RR were determined from a standard ECG (surface electrodes) used for triggering a rate meter, which provided a continuous recording of the heart periods (RR intervals).

All variables were recorded continuously on an eight-channel polygraph (model RS 3800, Gould Inc., Cleveland, OH, USA) and simultaneously stored on the hard disk of a conventional personal computer for further analysis after analog-to-digital conversion with a rate of 400 Hz. During anaesthesia, respiratory gases and vapour concentrations were measured continuously at the endotracheal tube orifice by infrared spectroscopy (Capnomac® Ultima SV, Datex-Engstrom, Helsinki, Finland). We also intermittently determined arterial blood gas tensions, oxygen saturation, and pH (ABL3®, Radiometer, Copenhagen, Denmark).

Derived variables

Heart rate variability

HR variability (HRV), an indicator of the activity of the autonomic nervous system, was studied as recommended.13 For this purpose, the original ECG signal, free of aberrant
ECG complexes and artefacts, was analysed during the last 5 min of each intervention (CHART®, ADInstruments, Castle Hill, Australia). HRV was analysed in the frequency domain and calculated as activity in the high frequency (HF: 0.15–0.5 Hz) and low frequency (LF: 0.04–0.15 Hz) range, the former showing predominantly vagal activity and the latter mainly sympathetic activity. Autonomic balance was assessed by calculating the quotient of power in the high frequency (nuHF) and low frequency (nuLF) range, respectively, divided by total power (sum of HF and LF power).

**Experimental protocol**

All experiments were carried out with awake dogs in the basal metabolic state (food withheld for 12 h with free access to water) and under standardized experimental conditions (lightly dimmed laboratory at thermoneutral temperature for dogs of 24°C). To ensure complete elimination of the inhalation anaesthetic, successive experiments were performed at least 1 week apart.

After instrumentation and connecting the animal to the recording system, we waited for 30 min until all variables had reached steady state. The experiments started with baseline measurements for a further 30 min while the animal breathed spontaneously. Following the insertion of the endotracheal tube (intravenous injection of propofol 3 mg kg⁻¹), the animal’s lungs were ventilated with 25% oxygen in nitrogen (tidal volume about 10 ml kg⁻¹ and a rate of 14 bpm to maintain normocarbia). Isoflurane was added and adjusted to an end-tidal concentration of 1.4% (1 MAC). We then waited 30 min in order to minimize interaction with propofol. During this equilibration period, a pulmonary artery catheter was advanced from the animal’s hind limb to obtain mixed venous blood samples. Thereafter, the following experiments were performed.

**Oxygen uptake during xenon anaesthesia (n=5)**

To evaluate whether xenon alters oxygen uptake, the following three mixtures were administered to each dog, but in a sequence which was randomized for each dog: \( \text{Fe's} = 1.4\% + \text{Fx} = 50\% \), \( \text{Fe's} = 1.4\% + \text{Fx} = 70\% \), \( \text{Fe's} = 2.8\% \). The randomization resulted in two of the six possible sequences being used in two dogs each and one in another dog. Each gas mixture was maintained for 20 min to reach steady state. Before the end of the experiment, the animal was ventilated again with isoflurane 1.4% (1 MAC) in air to check whether \( V_{O2} \) and CO returned to control values.

**Metabolic regulation of CO during xenon anaesthesia (n=5)**

In a second series of experiments on the same animals, the interventions of group 1 were repeated (with randomization leading to one of the six possible sequences being used in three dogs and one in two dogs) and extended by two additional mixtures: \( \text{Fe's} = 0.7\% + \text{Fx} = 50\% \), and \( \text{Fx} = 70\% \), always in that sequence. The total of five different mixtures was again administered between two periods of \( \text{Fe's} = 1.4\% \). Thus, we studied the dogs under a total of four interventions in the presence of xenon and under two different interventions with isoflurane, alone plus the awake state.

**Oxygen uptake during ganglionic blockade (n=5)**

After completion of groups 1 and 2, we studied the same animals again in order to see whether the increase in \( V_{O2} \) is of central or peripheral origin. For this purpose, hexamethonium, a ganglionic blocking agent, 7.5 mg kg⁻¹ was injected before induction of anaesthesia, followed by continuous infusion of 7.5 mg kg⁻¹ h⁻¹. Thereafter, the following two mixtures were administered to each dog: \( \text{Fe's} = 1.4\% + \text{Fx} = 50\% \), \( \text{Fe's} = 1.4\% + \text{Fx} = 70\% \), with randomization leading to one sequence being used in four dogs and the other in one dog.

**Data analysis and statistics**

Results are given as mean (SEM) and were compared using a paired t test. The resulting P values were corrected for multiple testing according to the Bonferroni procedure. In the case of repeated experiments in one animal, the results from individual dogs were averaged. CO was regressed on \( V_{O2} \) during the awake state and isoflurane anaesthesia, as well as during anaesthesia in the presence of xenon, and results were compared using an F test for differences between regression lines. The slopes of the individual relationships between \( V_{O2} \) and CO are given as mean slope and confidence interval. The effects on HR, MAP, systemic vascular resistance and C(a–vÅ)O₂ were compared by an analysis of variance for repeated measures (ANOVA), followed by Fisher’s protected least significant difference test if appropriate. Statistical significance was assumed when P<0.05.

**Results**

In general, \( V_{O2} \) increased significantly while CO remained essentially constant when xenon was added to isoflurane baseline anaesthesia. In detail, with the addition of xenon (50% and 70%) during isoflurane anaesthesia, \( V_{O2} \) increased from 3.4 (0.1) to 4.0 (0.1) and to 3.7 (0.2) ml kg⁻¹ min⁻¹ (P<0.05), respectively, whereas CO remained essentially unchanged (Fig. 1). In contrast, with the transition from awake to 1 MAC and eventually 2 MAC isoflurane alone, \( V_{O2} \) decreased by about 25% from 4.1 (0.2) ml kg⁻¹ min⁻¹ (awake) to 3.1 (0.1) ml kg⁻¹ min⁻¹ (2 MAC isoflurane). In parallel, CO decreased by about 40% from 121 (6) ml kg⁻¹ min⁻¹ (awake) to 70 (3) ml kg⁻¹ min⁻¹ (2 MAC isoflurane).

To answer the question of whether metabolic regulation of blood flow is maintained during xenon anaesthesia, we analysed the relationship between CO and \( V_{O2} \) in the presence and absence of xenon (Fig. 2). In both conditions, CO increased linearly with \( V_{O2} \) (\( r^2=0.97 \) and 0.94, respect-
ively) and the regression lines differed significantly \( (P<0.05) \). For any given CO, \( \dot{V}O_2 \) was 0.3–0.6 ml kg\(^{-1}\) min\(^{-1}\) greater in the presence of xenon. Conversely, CO is 14–21 ml kg\(^{-1}\) min\(^{-1}\) lower for a given \( \dot{V}O_2 \) when xenon is present.

To distinguish whether the increase in \( \dot{V}O_2 \) results from a central or peripheral effect, we analysed HRV to assess sympatovagal balance (see Fig. 3) and, in additional experiments, added xenon to the respiratory gases after ganglionic blockade (pretreatment with hexamethonium). After increasing anaesthetic depth with xenon or isoflurane, nuHF tended to increase and nuLF tended to decrease, indicating a shift towards vagal activation.

After ganglionic blockade (Fig. 4), \( \dot{V}O_2 \) increased during the addition of 50% or 70% xenon to 1.4% isoflurane anaesthesia from 3.4 (0.2) ml kg\(^{-1}\) min\(^{-1}\) to 4.0 (0.2) and 3.7 (0.3), respectively, whereas CO remained almost unchanged. Thus, in the presence or absence of ganglionic blockade, xenon elicited similar effects on \( \dot{V}O_2 \) and CO, albeit at a lower CO (compare with Fig. 1).

\( C(a-v\dot{V}O_2) \) tended to increase from 3.7 (0.2) ml 100 ml\(^{-1}\) during 1 MAC isoflurane anaesthesia to 4.1 (0.5) ml 100 ml\(^{-1}\) and finally 4.4 (0.5) ml 100 ml\(^{-1}\) with the addition of 50% and 70% xenon, respectively (Table 1). Nevertheless, \( C(a-v\dot{V}O_2) \) increased with increasing anaesthetic depth in a parallel manner in the presence and absence of xenon – except for 70% xenon alone (Fig. 5). However, the error bars show that, at any given MAC, the differences between isoflurane and xenon (with or without isoflurane) are not significant. It is worthy of note that HR (105 [5] beats min\(^{-1}\) during 1.4% isoflurane), decreased on the addition of xenon 50% and 70% to 95 (2) and 92 (2) beats min\(^{-1}\), respectively, which was in parallel with vagal activation, as indicated from the analysis of HRV (Fig. 3). Arterial pressure, however, did not change on the addition of xenon to 1.4% isoflurane anaesthesia.

**Discussion**

Our experiments show that, within the range of conditions studied, adding xenon to isoflurane baseline anaesthesia increases \( \dot{V}O_2 \). This increase in \( \dot{V}O_2 \) is independent of the autonomic nervous system and is probably caused by an increase in the cellular metabolic rate. Furthermore, metabolic regulation of blood flow is maintained during xenon anaesthesia, as shown by the linear relationship between CO and \( \dot{V}O_2 \). Accordingly, haemodynamic stability when adding xenon to isoflurane baseline anaesthesia is accompanied by an increase in the whole body metabolic rate (\( \dot{V}O_2 \)).

**Critique of methods**

Attempts to compare the effects of different anaesthetics on CO and \( \dot{V}O_2 \) rest primarily on the precision of the measurement methods. This question is of particular interest because \( \dot{V}O_2 \) during xenon anaesthesia has not been measured before.

\( \dot{V}O_2 \) was measured with the Deltatrac II at a precision of 3.5%. The precision is independent of the collection mode, flow through, or canopy,\(^{12,17,18}\) and is not influenced by the addition of volatile anaesthetics if a correction for the exhaled concentration of the anaesthetic is made.\(^{19}\) Moreover, the four times greater density of xenon\(^{4}\) compared with air did not alter the flow constant of the flow generator, and xenon did not influence oxygen – or carbon dioxide – measurements in our experiments. Accordingly, measurements of \( \dot{V}O_2 \) using a Deltatrac II were sufficiently precise to evaluate \( \dot{V}O_2 \) during anaesthesia with xenon in relationship to isoflurane.

CO was measured by ultrasound transit-time flow probes placed around the pulmonary artery. These probes had been
calibrated in vitro by a given saline flow and, after implantation, by the Fick principle from $\dot{V}O_2$ and $C(a-v)O_2$. Implantation around the pulmonary artery was chosen to obtain the entire cardiac output, which cannot be measured with flow probes placed around the aorta because coronary flow is not detected. These probes have been shown to continuously measure CO precisely over several years.9

The accuracy of our three independent measurement methods ($\dot{V}O_2$, CO and $C(a-v)O_2$) can be cross-checked...
using the Fick equation. Adding 50% xenon to 1.4% isoflurane did not change CO, so that changes in $\dot{V}_O_2$ and $C(a-v)O_2$ should balance each other. In fact, $\dot{V}_O_2$ and $C(a-v)O_2$ increased by 18% and 9%, respectively, confirming that CO was an essentially unchanged (calculation would yield 108%), with only 8% difference between independent measurement (ultrasound flowmetry) and calculation. This accuracy is likewise confirmed by the mean difference between measured and calculated $C(a-v)O_2$ values, which was only 3.9 (3.1)%.

Propofol, needed for inserting the endotracheal tube, may have influenced the effects of the inhalation anaesthetics. However, the plasma concentration of propofol should have decayed to a fraction of the initial peak within 10 min because of redistribution (half-life of the $\alpha$-phase of about 2 min) and, thereafter, more gradually as elimination continues (half-life of the $\gamma$-phase of about 4 h). Moreover, in pilot experiments, all dogs resumed their normal activity and behaviour within 15 min after the injection of a single dose of propofol. Accordingly, the additive anaesthetic effects of propofol should have been small, and comparable for all interventions.

The dosage of hexamethonium used in our study was appropriate to eliminate the influence of the autonomic nervous system, as indicated not only from the literature but also from our own experiments, in which arterial pressure and HR did not change after 45 s of bilateral carotid artery occlusion. In contrast, before hexamethonium administration, arterial pressure increased by about 40 mm Hg and HR by 20 beats min$^{-1}$. Thus, our methods should have been appropriate for deriving reliable measurements.

**Interpretation of results**

Metabolic regulation of blood flow manifests itself as a linear relationship between CO and $\dot{V}_O_2$, during both physiological conditions and inhalation anaesthesia.

![Fig 4 Oxygen consumption ($\dot{V}_O_2$) and cardiac output (CO) after ganglionic blockade with hexamethonium in the awake state, during 1.4% isoflurane anaesthesia alone and after adding 50% and 70% xenon to isoflurane baseline anaesthesia. Data are mean±SEM from five dogs. Note that $\dot{V}_O_2$ increased ($P<0.05$), whereas CO remained almost unchanged (n.s., not significant), as in the absence of ganglionic blockade (compare with Fig. 1).](image)

![Table 1 Haemodynamic variables and blood gas tensions in the awake state and during combinations of xenon and isoflurane anaesthesia in the intact dog and after ganglionic blockade with hexamethonium. Data are mean (SEM) from 15 experiments in five dogs. $P<0.05$ vs awake; $P<0.05$ vs 1.4% isoflurane (1st). HR, heart rate; MAP, mean arterial pressure; SVR, systemic vascular resistance; $P_{aO_2}$ and $P_{aCO_2}$, arterial oxygen and carbon dioxide gas tensions, respectively; $S_aO_2$, arterial oxygen saturation; $C(a-v)O_2$, mixed venous oxygen content difference](table)

<table>
<thead>
<tr>
<th>Isoflurane</th>
<th>Xenon</th>
<th>HR (beats min$^{-1}$)</th>
<th>MAP (mm Hg)</th>
<th>SVR (mm Hg litre$^{-1}$ min)</th>
<th>$P_{aO_2}$ (mm Hg)</th>
<th>$P_{aCO_2}$ (mm Hg)</th>
<th>pH</th>
<th>$S_aO_2$ (%)</th>
<th>$C(a-v)O_2$ (ml 100 ml$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact autonomic nervous system</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Awake</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.4 (1st)</td>
<td>82 (3)</td>
<td>98 (3)</td>
<td>25 (1)</td>
<td>94 (2)</td>
<td>37 (1)</td>
<td>7.35 (0.01)</td>
<td>95 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.4 (2nd)</td>
<td>110 (4)$^*$</td>
<td>71 (2)$^*$</td>
<td>21 (1)$^*$</td>
<td>126 (4)$^*$</td>
<td>41 (1)</td>
<td>7.31 (0.01)</td>
<td>97 (1)</td>
<td>3.7 (0.2)</td>
<td></td>
</tr>
<tr>
<td>2.8</td>
<td>102 (1)$^*$</td>
<td>42 (2)$^*$</td>
<td>19 (1)$^*$</td>
<td>119 (7)$^*$</td>
<td>41 (1)</td>
<td>7.30 (0.01)</td>
<td>97 (1)</td>
<td>5.1 (0.5)$^*$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>110 (4)$^*$</td>
<td>115 (3)$^*$</td>
<td>26 (1)$^*$</td>
<td>120 (2)$^*$</td>
<td>44 (1)</td>
<td>7.29 (0.02)</td>
<td>97 (1)</td>
<td>4.0 (0.4)$^*$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>107 (7)$^*$</td>
<td>21 (2)$^*$</td>
<td>116 (3)$^*$</td>
<td>43 (1)</td>
<td>7.29 (0.02)</td>
<td>96 (1)</td>
<td>3.3 (0.2)$^*$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>95 (2)$^*$</td>
<td>21 (1)$^*$</td>
<td>121 (6)$^*$</td>
<td>41 (1)</td>
<td>7.31 (0.01)</td>
<td>97 (1)</td>
<td>4.1 (0.5)$^*$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>70</td>
<td>92 (2)$^*$</td>
<td>23 (1)$^*$</td>
<td>121 (5)$^*$</td>
<td>42 (1)</td>
<td>7.29 (0.02)</td>
<td>97 (1)</td>
<td>4.1 (0.5)$^*$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>137 (4)</td>
<td>88 (3)</td>
<td>36 (3)</td>
<td>83 (4)</td>
<td>40 (2)</td>
<td>7.34 (0.01)</td>
<td>93 (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.4</td>
<td>117 (4)$^*$</td>
<td>27 (1)$^*$</td>
<td>124 (7)$^*$</td>
<td>38 (1)</td>
<td>7.34 (0.01)</td>
<td>97 (1)</td>
<td>3.8 (0.4)$^*$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.4</td>
<td>112 (4)$^*$</td>
<td>27 (3)$^*$</td>
<td>117 (5)$^*$</td>
<td>42 (1)</td>
<td>7.30 (0.01)</td>
<td>97 (1)</td>
<td>4.0 (0.4)$^*$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.4</td>
<td>111 (3)$^*$</td>
<td>26 (3)$^*$</td>
<td>115 (5)$^*$</td>
<td>43 (2)</td>
<td>7.29 (0.01)</td>
<td>96 (1)</td>
<td>4.0 (0.4)$^*$</td>
<td></td>
</tr>
</tbody>
</table>

Table 1 Haemodynamic variables and blood gas tensions in the awake state and during combinations of xenon and isoflurane anaesthesia in the intact dog and after ganglionic blockade with hexamethonium. Data are mean (SEM) from 15 experiments in five dogs. $P<0.05$ vs awake; $P<0.05$ vs 1.4% isoflurane (1st). HR, heart rate; MAP, mean arterial pressure; SVR, systemic vascular resistance; $P_{aO_2}$ and $P_{aCO_2}$, arterial oxygen and carbon dioxide gas tensions, respectively; $S_aO_2$, arterial oxygen saturation; $C(a-v)O_2$, mixed venous oxygen content difference
this context, $\dot{V}O_2$ is considered the independent variable and thus determines CO, and not vice versa.\cite{3} In our experiments during inhalation anaesthesia with isoflurane, CO and $\dot{V}O_2$ decreased from the awake state (basal metabolic conditions) to 2 MAC (points A–D in Fig. 2). This relationship was linear, with a slope of CO vs $\dot{V}O_2$ of 47, confirming our previous observations.\cite{3} In that study,\cite{3} we could also show that the relationship between CO and $\dot{V}O_2$ did not differ
significantly between the five most commonly used volatile anaesthetics.\(^3\)

In contrast to the effects of these volatile anaesthetics, increasing anaesthetic depth from 1 MAC isoflurane with xenon by about 0.5 MAC (MAC value of 119% in dogs\(^22\)) increased \(V_O_2\) while CO remained essentially unchanged. Cardiovascular stability during xenon anaesthesia has generally been observed in healthy individuals,\(^23\)\(^24\) as well as in dogs with dilated cardiomyopathy.\(^6\) Moreover, xenon had only minimal effects on myocardial contractility in vivo\(^5\)\(^25\) and maintained cardiovascular stability during surgical stimulation.\(^26\) However, total body oxygen consumption, the main determinant of CO, has not been measured during xenon anaesthesia before.

Increases in \(V_O_2\) could be related to either an increase in efferent sympathetic activity or a direct stimulating effect on the cellular metabolic rate. To test the contribution of the autonomic nervous system, we repeated the experiments after autonomic blockade. The increase in \(V_O_2\) during xenon anaesthesia was identical after ganglionic blockade, thus excluding increased sympathetic activity and suggesting a direct effect on cellular metabolic rate. However, there are no studies of the interaction between xenon and the molecular mechanisms of metabolism, and explanations of this phenomenon are beyond the scope of our experiments. The absence of sympathetic contribution to the increase in \(V_O_2\) is confirmed by the shift towards vagal activation, as indicated from the analysis of HRV in the experiments with the intact autonomic nervous system. Similar effects of xenon on the autonomic nervous system were previously observed in humans.\(^27\) In conclusion, xenon increases \(V_O_2\) most likely by directly stimulating the cellular metabolic rate.

Only myocardial oxygen consumption has been previously studied in detail during xenon anaesthesia, but this did not change either in vivo\(^25\) or in isolated hearts.\(^7\) However, myocardial oxygen consumption contributes only 10–15% to total body \(V_O_2\), and changes in myocardial oxygen consumption may not necessarily parallel changes in total body \(V_O_2\).

When anaesthetic depth changed, \(V_O_2\) and CO were linearly related in the presence of xenon, much like in the presence of volatile anaesthetics. However, the regression lines for xenon with and without isoflurane, and for isoflurane alone, differed significantly (Fig. 2). At any given CO, \(V_O_2\) was greater in the presence of xenon. If, in addition, CO and \(V_O_2\) are plotted against MAC, at least one more interpretation can be obtained (Fig. 6). Over the range of anaesthetic depths studied (below 2 MAC), substituting xenon for a proportion of the isoflurane (see arrows) would lead to an increase in CO and \(V_O_2\), with the effects of xenon tending to decrease as MAC increases. However, this interpretation has to be drawn with caution since it depends on the MAC of xenon, which has only been measured once in dogs\(^22\) and, in contrast to the other inhalation anaesthetics, differed by a factor of two between dogs and humans. It is also worth noting that HR decreased slightly during xenon anaesthesia in parallel with vagal activation, a phenomenon which has likewise been shown for the volatile anaesthetics.\(^28\) Thus, changes in HR during xenon anaesthesia are most likely caused by vagal activation. This interpretation is in accordance with the absence of this effect in isolated hearts.\(^7\) Accordingly, regulation of HR during xenon anaesthesia apparently does not differ from that during isoflurane anaesthesia.

In summary, adding xenon to isoflurane baseline anaesthesia increases \(V_O_2\), while haemodynamics, including CO, are essentially unchanged. Metabolic regulation of blood flow is maintained at a higher tissue oxygen extraction rate. When xenon is substituted for a proportion of the isoflurane, both \(V_O_2\) and CO are increased.

Acknowledgements

Xenon was provided by Messer Griessheim, Frankfurt, Germany. The authors thank Mrs B. Berke for her skilled assistance during experimentation and data analysis.

References

1 Barger AC, Richards V, Metcalfe J, Günter B. Regulation of the circulation during exercise — Cardiac output (direct Fick) and metabolic adjustment in the normal dog. Am J Physiol 1956; 184: 613–23


7 Stowe DF, Rehmert GC, Kwok WM, Weigt HU, Georgieff M, Bosnjak ZJ. Xenon does not alter cardiac function or major cation currents in isolated guinea pig hearts or myocytes. Anesthesiology 2000; 92: 516–22

8 vanLeersum E. Eine Methode zur Erleichterung der Blutdruckmessung bei Tieren. Pflügers Arch 1911; 142: 377–95


Eger Ell, Brandstater B, Saidman LJ, Regan MJ, Severinghaus JW, Munson ES. Equipotent alveolar concentrations of methoxyflurane, halothane, diethyl ether, fluroxene, cyclopropane, xenon and nitrous oxide in the dog. Anesthesiology 1965; 26: 771–7


Picker O, Scheeren TWL, Arndt JO. Inhalation anaesthetics increase heart rate by decreasing cardiac vagal activity in dogs. Br J Anaesth 2001; 87: 748–54