Xenon produces minimal haemodynamic effects in rabbits with chronically compromised left ventricular function

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Background. Xenon has only minimal haemodynamic side-effects on normal myocardium and might be a preferable anaesthetic agent for patients with heart failure. We studied the haemodynamic changes caused by 70% xenon in rabbits with chronically compromised left ventricular (LV) function.

Methods. Anaesthetized rabbits were thoracotomized and a major coronary artery was ligated to induce ischaemic heart disease. Nine weeks later, rabbits were again anaesthetized (ketamine/propofol), and haemodynamics were measured during inhalation of 70% xenon using echocardiography [LV end-diastolic dimension (LVedD), fractional shortening (FS), velocity of circumferential fibre shortening (VcF), ejection fraction (EF)] in closed-chest animals. Subsequently, rabbits were thoracotomized and instrumented for measurement of LV pressure (tip manometer), LV \( \frac{dP}{dt_{max}} \) and cardiac output (ultrasonic flow probe). Haemodynamics were recorded again during inhalation of 70% xenon.

Results. All rabbits had compromised LV function 9 weeks after coronary artery ligation. Mean LVedD increased from 12.9 (SD 0.9) mm to 17.1 (0.4) mm; EF decreased from 73 (9) to 64 (8)%; FS decreased from 36 (7) to 29 (5)%; VcF decreased from 28.9 (6.8) to 17.6 (4.7) mm s\(^{-1}\); all \( P<0.05 \). Inhalation of 70% xenon had no effect on haemodynamics in closed-chest rabbits, as measured by echocardiography. After invasive instrumentation, small decreases in LV pressure from 78 (20) to 72 (19) mm Hg, LV \( \frac{dP}{dt_{max}} \) from 3081 (592) to 2633 (503) mm Hg s\(^{-1}\) and cardiac output from 239 (69) to 225 (71) ml min\(^{-1}\) were observed during xenon inhalation (all \( P<0.05 \)).

Conclusion. These data show that xenon has only minimal negative inotropic effects in rabbits with LV dysfunction after coronary artery ligation.

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The anaesthetic properties of xenon may make this noble gas an interesting adjunct to general anaesthesia. Several previous studies focused on the cardiovascular side-effects of xenon.1–4 In humans, fractional area change obtained by echocardiography was not altered by 65% xenon.1 No significant effect on arterial blood pressure could be observed in patients anaesthetized with 70% xenon in comparison with 70% nitrous oxide.3 In pentobarbital-anaesthetized pigs, cardiac index, central venous pressure, aortic pressure (AOP) and systemic vascular resistance (SVR) were not significantly altered by 30–70% xenon.5 During xenon anaesthesia, a tendency to decreased heart rate accompanied by an increased variability of the cardiac rhythm was observed.1,2,6 Recently, we demonstrated by direct intracoronary administration in dogs that xenon has a small but consistent direct negative inotropic effect.7 The minimal cardiovascular effects of xenon are in contrast to the marked haemodynamic effects of other
available inhalational anaesthetics. There are few data regarding the haemodynamic effects of xenon in pathophysiological myocardial conditions. Xenon reduced reperfusion injury after regional myocardial ischaemia in rabbits in vivo. In isoflurane-anaesthetized dogs with dilated cardiomyopathy, addition of xenon decreased heart rate and increased the time constant of isovolumic relaxation. In these experiments, no alterations of arterial or left ventricular (LV) pressures or indices of LV preload and afterload were observed.

The current study investigates the haemodynamic changes during 70% xenon inhalation in rabbits with compromised LV function after ligation of a major coronary artery.

Materials and methods
The current study conforms with the Home Office Guidance on the Operation of Animals (Scientific Procedures) Act 1986, published by Her Majesty’s Stationary Office in London, and was performed in accordance with the regulations of the Law on the Protection of Animals and local institutional regulations.

Induction of chronic LV dysfunction
New Zealand white rabbits were anaesthetized with intramuscular xylazine (6 mg kg⁻¹) and ketamine (6 mg kg⁻¹), followed by intravenous propofol (12 mg kg⁻¹). The trachea was intubated (tube 3.0 mm internal diameter) and the lungs were ventilated using a Harvard rodent ventilator (Model 683, Harvard, South Natick, MA) at a frequency of 30–35 bpm and a tidal volume of 15–20 ml in order to maintain end-expiratory CO₂ at approximately 35 mm Hg (Datex Ohmeda 5250 R6M, Division of Instrumentarium, Helsinki, Finland). Anaesthesia was maintained by inhalation of isoflurane (2–4 vol%) and nitrous oxide (50 vol%). Surface ECG was recorded continuously.

All surgical procedures were performed under sterile conditions, and intravenous antibiotic prophylaxis (cephazolin 35 mg kg⁻¹) was given. The chest was opened by a left thoracotomy in the fourth intercostal space, and a small incision made in the pericardium. The left anterior descending coronary artery was occluded with a 5-0 prolene suture (Ethicon 5/0, 1-metric, TF). The effectiveness of this manoeuvre was verified by the appearance of epicardial cyanosis and ECG changes. Ventricular fibrillation in the first 15 min after coronary artery occlusion was treated by electrical defibrillation (5 J, DCS261 Defibrillator, Piekser, Ratingen, Germany). Fifteen min after coronary artery occlusion, the chest wound was closed in layers and air aspirated from the thorax. Postoperative analgesia and antibiotic prophylaxis were given by subcutaneous injection of metamizole (30 mg kg⁻¹) and amoxicillin (15 mg kg⁻¹), respectively. A vest (rabbit jacket size M, Byron, Grand Island, NY) covered the wound.

Echocardiography
Before coronary artery occlusion and weekly thereafter, rabbits were anaesthetized with ketamine/xylazine and were allowed to breath spontaneously. The chest was shaved and animals were placed in the left lateral decubitus position on a warming pad to maintain normothermia.

Echocardiograms were performed with an HDI 3000 ultrasonograph (ATL, Solingen, Germany). A dynamically 5–8 MHz convex array transducer was placed on a layer of acoustic coupling gel applied to the left hemithorax. Short- and long-axis views of the left ventricle were obtained by slight angulation and rotation of the transducer. Two-dimensional targeted M-mode studies were obtained at the level of the papillary muscles. Anterior and posterior end-diastolic and end-systolic wall thickness and LV internal dimension were determined according to the leading-edge convention of the American Society of Echocardiography.

LV fractional shortening (FS) was calculated as: FS = (EDD – ESD)/EDD where EDD and ESD represent LV end-diastolic and end-systolic dimension, respectively. Spectral Doppler waveforms were analysed for aortic, pulmonary artery, and peak early and late-diastolic transmitral velocities. Cardiac output (CO) was calculated echocardiographically from pulmonary artery flow. All measurements were made from original tracings and three beats were averaged for each measurement.

Invasive measurements
For measurement of AOP, a 20-gauge Teflon catheter was introduced from the left carotid artery into the aortic arch and connected to a pressure transducer (Statham transducer, PD23, Gould, Cleveland, OH). The external jugular vein was cannulated and animals received a continuous infusion of normal saline 15 ml kg⁻¹ h⁻¹ to compensate for fluid losses. After median sternotomy and pericardiectomy, an ultrasonic flow probe was placed around the ascending aorta in order to measure LV stroke volume minus coronary flow volume (4S ultrasonic flow probe, T 208, Transonic Systems Inc., Ithaca, NY). LV pressure was monitored using a catheter-tip manometer (Micro-Tip Pressure Transducer, SPC-350/SF, Millar Instruments, Houston, TX) introduced via the left atrium. After completion of the preparation, the thoracotomy was covered with plastic film to minimize evaporative and convective heat loss.

Experimental programme
Nine weeks after induction of chronic ischaemic heart disease, rabbits were anaesthetized with ketamine/xylazine followed by a continuous infusion of propofol (1.2 mg kg⁻¹ min⁻¹) and were intubated and ventilated with 30% oxygen
in air, as described above. Echocardiographic measurements were performed during baseline conditions and after 15 min inhalation of 70% xenon with 30% oxygen.

Fifteen min after completion of the preparation for invasive measurements, baseline values were determined and the rabbits again inhaled 70% xenon with 30% oxygen for 15 min. Another 15 min were allowed to wash out the noble gas and then isoflurane (1.2 vol%) was added to the inspired gas to ensure that the experimental model used was suitable to detect haemodynamic changes caused by inhalational anaesthetics.

At the end of the experiment, the heart was arrested by injection of potassium chloride solution into the left atrium, quickly excised and further processed to determine infarct size as described previously.10

Data analysis

LV pressure, its first derivative $dP/dt$, AOP, and stroke volume were continuously recorded on a personal computer (AcqKnowledge III, BIOPAC Systems Inc, Goleta, CA). Global systolic function was measured in terms of LV peak systolic pressure (LVPSP) and the first derivative of LV pressure, LV $dP/dt_{\text{max}}$. CO was calculated from stroke volume and heart rate, rate pressure product (RPP) from heart rate and LVPSP, and SVR from mean AOP and CO, assuming a right atrial pressure of 0 mm Hg in the open-chest preparation.

Measured values are presented as mean (SD). Statistical analysis was performed by Student’s $t$ test for paired observations (baseline values before and after coronary artery ligation and values before and after xenon inhalation). All comparisons were two-tailed and a $P$ value <0.05 was regarded as significant.

Results

A total of 15 animals was used. Three animals died from recurrent ventricular fibrillation after coronary artery occlusion.

Development of LV dysfunction

Development of chronic LV dysfunction was measured weekly by echocardiography. Nine weeks after coronary artery occlusion, no further changes could be observed. Body weight increased during this time from 2.7 (0.3) to 3.3 (0.8) kg ($P<0.05$). Echocardiographic measurements showed an increase in LVedD and a decrease in myocardial function (Figure 1). Aortic flow velocity decreased from 96.4 (17.2) to 67.1 (12.9) cm s$^{-1}$ ($P<0.05$) and CO (determined by echocardiography) from 226 (19) to 193 (36) ml min$^{-1}$ ($P=0.14$).

Xenon in rabbits with LV dysfunction

No significant changes in global haemodynamics could be determined by echocardiography during inhalation of 70% xenon (Figure 2). After invasive instrumentation, xenon inhalation resulted in a small but consistent decrease of LV pressure, $dP/dt_{\text{max}}$, and CO (Figure 3). Because heart rate did not change during xenon inhalation (baseline: 201 [23] beats min$^{-1}$; xenon: 202 [27] beats min$^{-1}$), RPP was altered in parallel to changes in LVP (baseline: 15.6 [4.6] mm Hg 10$^3$ min$^{-1}$; xenon: 14.5 [4.6] mm Hg 10$^3$ min$^{-1}$, $P<0.001$). Inhalation of 70% xenon had no effect on SVR (baseline: 274 [57] mm Hg min ml$^{-1}$; xenon: 264 [77] mm Hg min ml$^{-1}$, $P=0.5$).

To ensure that changes in haemodynamics could be determined with the method used, seven rabbits received
isoflurane 1.2 vol% at the end of the experiment. Inhalation of isoflurane produced a marked reduction of global haemodynamics by 18–44% of baseline values (Table 1).

Discussion

The main finding of the present study is that 70% xenon produces only minimal effects on cardiovascular function in rabbits with compromised LV function after chronic ischaemia. These findings underline the favourable haemodynamic profile of xenon even in the presence of chronic ischaemic heart disease.

Critique of methods

Several methods have been described to induce heart failure in rabbits, such as chronic congestive heart failure after rapid ventricular pacing, cardiomyopathy after adriamycin administration, double pressure and volume overload or permanent coronary artery occlusion. We used ligation of a major coronary artery because ischaemic heart disease is the most common clinical cause for heart failure. However, with this model, only moderate LV dysfunction was achieved, as demonstrated by a decrease in myocardial function of 12–37% (Figure 1). Therefore, conclusions about haemodynamic stability during xenon inhalation must be limited to the situation of compromised LV function after coronary artery ligation. The effects of xenon on haemodynamics during severe congestive heart failure may be different. The site of coronary artery occlusion was the long axis of the left ventricle towards the apex approximately one-quarter of the distance from the atrioventricular groove to the LV apex. Increasing the size of the ischaemic area in this experimental model is not possible because a more proximal coronary occlusion results in unresolvable ventricular fibrillation and death.

Experiments were performed during baseline anaesthesia with ketamine and propofol. It cannot be excluded that, with different anaesthetic supplements or in other species, xenon may have different haemodynamic effects on failing myocardium.

We used xenon at a concentration of 70%. During inhalation and after recovery from xenon, no changes in arterial oxygen partial pressure were observed and it can therefore be concluded that hypoxia did not occur. Calzia et al. demonstrated that diffusion hypoxia is unlikely to occur during recovery from xenon anaesthesia.

Only one concentration of xenon was used and the findings must be limited to this concentration. For the rabbit, the exact minimal alveolar concentration (MAC) has not yet been determined. In dogs, the MAC of xenon is super-atmospheric at 119% and in humans, 71%. This MAC value has recently been confirmed in humans. Taking the MAC values of the commonly used volatile anaesthetics in humans, dogs and rabbits, and relating these values to the MAC of xenon, it is likely that the MAC of xenon in rabbits is about 120%. Therefore, 70% xenon might represent only 0.6 MAC in rabbits. The isoflurane concentration used is comparable to 0.6 MAC (2.0 vol% isoflurane = 1 MAC).

Interpretation of results

Xenon can be used as an anaesthetic adjunct and it has been frequently reported that this noble gas produces only minimal effects on cardiovascular function. Our knowledge of the effects of xenon at the cellular and molecular level is still limited. Recently, Stowe et al. demonstrated that xenon does not alter cardiac function in isolated guinea-pig hearts. In isolated cardiomyocytes, the amplitudes of the Na+, L-type Ca2+, and the inward-rectifier K+ channels were not altered by xenon up to 80%. These data suggest that xenon does not affect the cardiac action potential. In a previous study from our laboratory we showed that xenon, given directly to the myocardium by intracoronary administration, exerts a small but consistent direct negative inotropic effect in the dog heart in vivo, reducing variables of regional myocardial contractility by 5–8%. However, these changes seemed to be negligible in comparison with
The inotropic effects caused by other volatile anaesthetics. In chronically instrumented dogs, cardiovascular stability was accompanied by an increase in total body oxygen consumption. In rats, the relationship between regional cerebral blood flow and cerebral glucose utilization is maintained during xenon anaesthesia, although reset at a higher level. These data suggest that xenon increases organ blood flow. Myocardial blood flow was not measured in the present study; therefore, changes in myocardial oxygen delivery and consumption cannot be excluded.

Few data are available regarding the cardiovascular effects of xenon in pathophysiological states such as myocardial ischaemia or cardiomyopathy. In isoflurane-anesthetized dogs with experimentally dilated cardiomyopathy, Hettrick and co-workers found that xenon had only minimal cardiovascular effects. In these experiments, xenon decreased heart rate and increased the time constant of isovolumetric relaxation while having no effect on variables of preload and afterload. Xenon administration during reperfusion after coronary artery occlusion reduced myocardial reperfusion injury in rabbits. In the presence of regional myocardial ischaemia and reperfusion, xenon produced a small reduction in CO and an increase in mean AOP, resulting in an increase in SVR. This effect was rapidly reversible after discontinuation of xenon. In contrast, in healthy patients no haemodynamic changes during xenon anaesthesia as assessed by echocardiography were reported. The present data are in accordance with these previous findings, showing that the haemodynamic changes caused by xenon are too small to be detected by echocardiography (Figure 2). Invasive measurements revealed a slight negative inotropic action of the noble gas in rabbits with compromised LV function (Figure 3), but this effect was very small, at least in comparison with isoflurane (Table 1).

Table 1  Haemodynamic changes during inhalation of isoflurane 1.2 vol% in rabbits with chronically compromised LV function. Data are mean (SD), n=7; *P<0.01; **P<0.001 vs baseline. LVP=left ventricular pressure; dP/dt max and dP/dt min=peak positive and negative velocity, respectively, of the change of LVP.

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<tr>
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<th>Baseline</th>
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<tr>
<td>Heart rate (beats min⁻¹)</td>
<td>200 (20)</td>
<td>193 (9)</td>
</tr>
<tr>
<td>LVP (mm Hg)</td>
<td>64 (9)</td>
<td>46 (8)</td>
</tr>
<tr>
<td>dP/dt max (mm Hg s⁻¹)</td>
<td>3015 (672)</td>
<td>1690 (408)**</td>
</tr>
<tr>
<td>dP/dt min (mm Hg s⁻¹)</td>
<td>-2256 (388)</td>
<td>-1277 (310)**</td>
</tr>
<tr>
<td>Cardiac output (ml min⁻¹)</td>
<td>193 (40)</td>
<td>153 (37)**</td>
</tr>
<tr>
<td>Systemic vascular resistance (mm Hg min ml⁻¹)</td>
<td>295 (42)</td>
<td>241 (31)**</td>
</tr>
<tr>
<td>Rate pressure product (mm Hg 10⁵ min⁻¹)</td>
<td>12.7 (1.3)</td>
<td>8.8 (1.4)**</td>
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In summary, our data show that xenon has minimal effects on global haemodynamics in rabbits with compromised LV function after coronary artery ligation. Because of its considerable cost and limited availability, xenon anaesthesia might not achieve widespread clinical use, but may be a useful alternative in selected patients. Xenon anaesthesia may be beneficial for patients with cardiac disease who cannot tolerate the depressant effects of other commonly used anaesthetics.

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Xenon inhalation and left ventricular dysfunction

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