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## ***Xenon Does Not Alter Cardiac Function or Major Cation Currents in Isolated Guinea Pig Hearts or Myocytes***

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**Background:** The noble gas xenon (Xe) has been used as an inhalational anesthetic agent in clinical trials with little or no physiologic side effects. Like nitrous oxide, Xe is believed to exert minimal unwanted cardiovascular effects, and like nitrous oxide, the vapor concentration to achieve 1 minimum alveolar concentration (MAC) for Xe in humans is high, *i.e.*, 70–80%. In the current study, concentrations of up to 80% Xe were examined for possible myocardial effects in isolated, erythrocyte-perfused guinea pig hearts and for possible effects on altering major cation currents in isolated guinea pig cardiomyocytes.

**Methods:** Isolated guinea pigs hearts were perfused at 70 mmHg *via* the Langendorff technique initially with a salt solution at 37°C. Hearts were then perfused with fresh filtered (40- $\mu$ m pore) and washed canine erythrocytes diluted in the salt solution equilibrated with 20% O<sub>2</sub> in nitrogen (control), with 20% O<sub>2</sub>, 40% Xe, and 40% N<sub>2</sub>, (0.5 MAC), or with 20% O<sub>2</sub> and 80% Xe (1 MAC), respectively. Hearts were perfused with

80% Xe for 15 min, and bradykinin was injected into the blood perfusate to test endothelium-dependent vasodilatory responses. Using the whole-cell patch-clamp technique, 80% Xe was tested for effects on the cardiac ion currents, the Na<sup>+</sup>, the L-type Ca<sup>2+</sup>, and the inward-rectifier K<sup>+</sup> channel, in guinea pig myocytes suffused with a salt solution equilibrated with the same combinations of Xe, oxygen, and nitrogen as above.

**Results:** In isolated hearts, heart rate, atrioventricular conduction time, left ventricular pressure, coronary flow, oxygen extraction, oxygen consumption, cardiac efficiency, and flow responses to bradykinin were not significantly (repeated measures analysis of variance, *P* > 0.05) altered by 40% or 80% Xe compared with controls. In isolated cardiomyocytes, the amplitudes of the Na<sup>+</sup>, the L-type Ca<sup>2+</sup>, and the inward-rectifier K<sup>+</sup> channel over a range of voltages also were not altered by 80% Xe compared with controls.

**Conclusions:** Unlike hydrocarbon-based gaseous anesthetics, Xe does not significantly alter any measured electrical, mechanical, or metabolic factors, or the nitric oxide-dependent flow response in isolated hearts, at least partly because Xe does not alter the major cation currents as shown here for cardiac myocytes. The authors' results indicate that Xe, at approximately 1 MAC for humans, has no physiologically important effects on the guinea pig heart. (Key words: Cardiac efficiency; halothane; ion currents; left ventricular pressure; sevoflurane.)

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INERT noble gases are long recognized to have anesthetic properties. Inhalation of compressed air during diving was found to cause formation of nitrogen gas emboli in body spaces on ascent to the surface to a degree that pain and death could result. Substitution of inert gases, such as argon, for nitrogen greatly reduced the incidence of the "bends."<sup>1</sup> Interestingly, it was discovered that inert-gas substitution caused divers to become nauseous and drowsy on return to the surface; thus, it was suspected that inert gases might have anesthetic properties. This was later confirmed, and xenon (Xe) was found to have the most potent anesthetic capability of the inert gases.<sup>2–4</sup>

Xenon has recently attracted renewed interest because it possesses many of the characteristics of an ideal anesthetic.<sup>5</sup> Its minimum alveolar concentration (MAC) is 71% in humans,<sup>2–4,6</sup> indicating that it is a moderately more potent

anesthetic than is nitrous oxide ( $\text{N}_2\text{O}$ ; MAC = 104%). As an inert gas, Xe is odorless, nonexplosive, nonpungent, and does not form covalent bonds except under extreme conditions. Furthermore, unlike other general anesthetics, it is environmentally friendly because it is prepared by fractional distillation of atmospheric air, usually as a byproduct of steel-making in blast furnaces.

Xenon has successfully been used as an anesthetic in clinical trials.<sup>7-12</sup> Its very low blood:gas partition coefficient of 0.14 allows precise corrections of anesthetic depth and a rapid induction and emergence.<sup>6</sup> Improved scavenging and recycling techniques<sup>9,13</sup> for Xe now permit its use in clinical anesthesia. Xe is believed to lack the occupational and environmental hazards attributed to  $\text{N}_2\text{O}$  and hydrocarbon-based volatile anesthetics.<sup>2-4</sup>

Although nonpolar, Xe preferentially interacts with the amphiphilic head region of the lipid membrane.<sup>14</sup> This suggests that Xe could exert cellular effects by a weak interaction with other molecules. One aim was to investigate if Xe has any depressant or stimulatory myocardial effects when given at clinically relevant concentrations in the isolated, erythrocyte-perfused guinea pig heart preparation. Because cationic fluxes in cardiac myocytes are largely responsible for cardiac function, the other aim was to investigate the effects of Xe on the major cation currents, the  $\text{Na}^+$  ( $I_{\text{Na}}$ ), the L-type  $\text{Ca}^{2+}$  ( $I_{\text{Ca,L}}$ ), or the inward-rectifier  $\text{K}^+$  ( $I_{\text{Kir}}$ ) channel. This is the first study to examine directly the effects of Xe on cardiac function and on the major cation currents that are responsible for maintaining the cardiac action potential.

## Materials and Methods

### *Langendorff Heart Preparation*

The investigation conformed to the *Guide for the Care and Use of Laboratory Animals* published by the U.S. National Institutes of Health (NIH publication no. 85-23, revised 1996). After approval was obtained from the institutional animal studies committee at the Medical College of Wisconsin, 25 mg ketamine and 1,000 U heparin were injected intraperitoneally into 16 albino English short-haired guinea pigs (250–300 g). The description of the surgical preparation for this model has been reported in detail previously.<sup>15-18</sup> Each heart was perfused in retrograde fashion through the aorta at 70 mmHg with cold, oxygenated, modified Krebs-Ringer's solution ( $\text{CaCl}_2$  1.25 mM) as described previously. Isovolumetric left ventricular (LV) pressure, coronary flow, and spontaneous heart rate were measured continuously as described previously.<sup>15-18</sup>

Coronary sinus effluent was collected by placing a small, gas-impermeable cannula into the right ventricle through the pulmonary artery after ligating the superior and inferior venae cavae. Coronary outflow (coronary sinus) oxygen tension and pH were measured continuously on-line with a miniature thermostable Clark oxygen electrode (Model 203B; Insteck Laboratories, Plymouth Meeting, PA) and temperature-compensated pH electrode (microcomputer pro-vision pH meter, model 05669-20, pH electrode PHE 2121; Cole Palmer Instruments, Vernon Hills, IL). Perfusate, bath, and the oxygen electrode temperatures were maintained precisely at  $37.2 \pm 0.1^\circ\text{C}$  using a thermostatically controlled water circulator *via* jacketed glass tubing, bath, and aluminum heat exchangers. Coronary inflow and effluent pH and oxygen and carbon dioxide tensions were measured off-line at  $37^\circ\text{C}$  with an intermittently self-calibrating analyzer system (Radiometer ABL-2; Medtron Chicago, Inc., Des Plaines, IL).

Percent oxygen extraction was calculated as the difference between inflow and outflow tensions multiplied by 100 and divided by inflow oxygen tension. Percent oxygen extraction was measured in all studies to assess direct vasodilatory responses separate from those caused by an autoregulatory response that may result from altered contractility. This measurement assumes that local metabolites are produced in proportion to myocardial oxygen consumption and that local metabolites are major factors controlling autoregulation of coronary flow. Oxygen tension of the inflow perfusate ( $155 \pm 6$  mmHg) was kept constant by maintaining the pressure in the reservoir container 5 mmHg above atmospheric pressure. Myocardial oxygen consumption was calculated as coronary flow times the arterial-venous oxygen content based on the hemoglobin concentration (approximately 2.8 g/100 ml) and oxygen binding of 1.34 ml  $\text{O}_2$ /g hemoglobin. Cardiac efficiency was calculated as LV pressure times heart rate divided by myocardial oxygen consumption. Spontaneous heart rate, outflow oxygen tension (mmHg), coronary flow, and systolic and diastolic isovolumetric LV pressure were displayed continuously on a fast-writing (3 kHz), high-resolution, eight-channel chart recorder (Astro-Med Inc., West Warwick, RI).

After baseline control values were obtained, all hearts were gravity perfused at a constant pressure of 70 mmHg with freshly filtered (40- $\mu\text{m}$  pore) and triple saline-washed canine erythrocytes diluted in Krebs-Ringer's solution after mixing with 20%  $\text{O}_2$  in nitrogen (control). Erythrocyte perfusion was necessary to attain a higher oxygen-carrying capacity because each heart had to be

perfused with solution equilibrated with an oxygen fraction of only 0.2, with the balance a combination of nitrogen and/or Xe. Arterial values were as follows: hematocrit,  $7.5 \pm 0.4\%$  (SEM); oxygen saturation,  $100 \pm 0\%$ ;  $\text{Na}^+$ ,  $142.2 \pm 1.3$  mM;  $\text{K}^+$ ,  $4.2 \pm 0.0$  mM; and  $\text{Ca}^{2+}$ ,  $1.2 \pm 0.0$  mM. Trial studies with erythrocytes showed that a hematocrit of  $> 5\%$  did not enhance isolated cardiac performance at an oxygen fraction of 0.2. The presence of Xe had no effect on these values. Xe MAC for the guinea pig is unknown. Xe concentrations of approximately 0.5 and 1 MAC for humans were prepared by equilibrating the perfusate with 20%  $\text{O}_2$ , 40% Xe, and 40%  $\text{N}_2$ , or with 20%  $\text{O}_2$  and 80% Xe, respectively. These gas mixtures were prepared by injecting known volumes of the gases into evacuated gas reservoir bags and verifying that the oxygen and nitrogen fractions, measured *via* mass spectroscopy, were approximately 20% and 40% or 20% and 0%, respectively. Arterial oxygen tensions were  $159 \pm 7$  mmHg for controls,  $155 \pm 6$  mmHg for 40% Xe,  $156 \pm 6$  mmHg for 80% Xe, and  $155 \pm 5$  mmHg for postcontrols.

#### Protocol

After a period of stabilization, adenosine (200  $\mu\text{l}$  from a 200- $\mu\text{M}$  stock solution) was injected directly into the aortic root cannula to determine initial maximal coronary flow during Krebs-Ringer's perfusion. Ten minutes after initiating perfusion with the erythrocyte-Krebs-Ringer's solution (control), each heart was perfused for 15 min in random order with either concentration of Xe preequilibrated in the erythrocyte-Krebs-Ringer's solution. Endothelium-dependent flow responses<sup>19,20</sup> to bradykinin were tested in the presence and absence of Xe to assess if vasodilatory capacity is altered by Xe as it may be with volatile anesthetics. Bradykinin (100  $\mu\text{l}$  from 10 nM and 1  $\mu\text{M}$  stock solutions) was injected directly into the aortic root cannula during erythrocyte-Krebs-Ringer's perfusion before and during exposure to 80% Xe. Adenosine was again injected at the end of each experiment at the same concentration to observe any change in maximal coronary flow. A Xe-free control period was interspersed between each Xe treatment.

#### Patch Clamp Studies

**Cell Isolation.** Single cardiac myocytes were isolated from ventricles of guinea pigs weighing 200–300 g. The cell isolation procedure has been described previously.<sup>21–24</sup> Guinea pigs were first injected intraperitoneally with sodium pentobarbital (70 mg/kg) and 1,000 U heparin. During deep anesthesia, the thoracic cavities were opened, and

the hearts were quickly excised. The hearts were then mounted on a Langendorff apparatus and perfused in retrograde fashion *via* the aorta with an oxygenated buffer solution containing Joklik (minimum essential medium; Gibco, Life Technologies, Gaithersburg, MD). After blood was cleared from the hearts, they were perfused for approximately 14 min in an enzyme solution containing Joklik, 0.4 mg/ml collagenase (Type II; Gibco) and 0.17 mg/ml protease (Type XIV; Sigma, St. Louis, MO). The digested ventricular tissue was then chopped coarsely into small fragments and shaken in a water bath for further dispersion. The dispersed cells were filtered, centrifuged, and washed in a recovery solution containing Joklik, 1 mM  $\text{CaCl}_2$ , and 1 g/100 ml bovine albumin fraction V (Serologicals, Milwaukee, WI). Additional washing in Tyrode's solution was performed before the cells were ready for experiments. Only rod-shaped cells with clear borders and striations were selected for experiments, and they were used within 12 h of isolation.

**Solutions.** High-resistance seals and voltage clamp were attained in Tyrode's solution containing 132 mM NaCl, 4.8 mM KCl, 1.2 mM  $\text{MgCl}_2$ , 10 mM HEPES, 5 mM glucose, and 1 mM  $\text{CaCl}_2$  with pH adjusted to 7.4 with NaOH. After voltage clamp was established, the external bath solution was changed to a solution that isolated either the  $I_{\text{Na}}$ , the  $I_{\text{Ca,L}}$ , or the  $I_{\text{Kir}}$  channel current. The bath solution for recording  $I_{\text{Na}}$  contained 115 mM CsCl, 10 mM NaCl, 10 mM HEPES, 1 mM  $\text{MgCl}_2$ , 1.8 mM  $\text{CaCl}_2$ , 5.5 mM glucose, and 3 mM  $\text{CoCl}_2$  to block  $I_{\text{Ca,L}}$ . The pH was adjusted to 7.2 with CsOH. For  $I_{\text{Ca,L}}$ , the sodium-free bath solution contained 132 mM *N*-methyl-D-glucamine, 2 mM  $\text{CaCl}_2$ , 4.8 mM CsCl, 2 mM  $\text{MgCl}_2$ , 10 mM HEPES, and 5 mM glucose, with pH adjusted to 7.4 with HCl. For  $I_{\text{Kir}}$ , the bath solution contained 132 mM *N*-methyl-D-glucamine, 1 mM  $\text{CaCl}_2$ , 2 mM  $\text{MgCl}_2$ , 5 mM KCl, 10 mM HEPES, and 5 mM glucose, with pH adjusted to 7.4 with HCl.  $\text{CdCl}_2$ , 200  $\mu\text{M}$ , was also included to block  $I_{\text{Ca,L}}$ . The corresponding pipette solutions for each current recording were as follows. For  $I_{\text{Ca,L}}$ , the solution contained 110 mM CsCl, 10 mM HEPES, 1 mM  $\text{MgCl}_2$ , 1 mM  $\text{CaCl}_2$ , 11 mM EGTA, 5 mM  $\text{K}_2\text{ATP}$ , and pH adjusted to 7.3 with CsOH. For  $I_{\text{Na}}$ , the solution contained 90 mM CsF, 60 mM CsCl, 10 mM NaF, 1 mM  $\text{CaCl}_2$ , 2 mM  $\text{MgATP}$ , 10 mM HEPES, 11 mM EGTA, and pH adjusted to 7.3 with CsOH. Finally, for  $I_{\text{Kir}}$ , the solution contained 50 mM KCl, 60 mM K-glutamate, 1 mM  $\text{MgCl}_2$ , 1 mM  $\text{CaCl}_2$ , 5 mM  $\text{K}_2\text{ATP}$ , 10 mM HEPES, 11 mM EGTA, and pH adjusted to 7.3 with KOH.

At least 1 MAC of each of three different anesthetics, Xe, sevoflurane, and halothane, were examined. Xe was provided by Messer-Griesheim AG (Duisburg, Germany). Sevoflurane

(Maruishi Pharmaceutical, Osaka, Japan) was obtained from Abbott Laboratories (North Chicago, IL), and halothane was obtained from Halocarbon Laboratories (River Edge, NJ). The anesthetics were contained in glass syringes and delivered *via* a peristaltic pump. Loss of anesthetics was minimized by using Teflon (Cole-Parmer, Vernon Hills, IL) tubing for the delivery system and by selecting cells close to the inflow mouth of the recording chamber. For sevoflurane and halothane, anesthetic concentrations in the chamber were determined by standard gas chromatography after each experiment as noted previously.<sup>21,22</sup> The Xe gas mixture was prepared by injecting known volumes of Xe, oxygen, and external bath solution into evacuated airtight gas reservoir bags in a manner like that for the isolated heart studies. The volume ratio of gas to solution was set to 10 to ensure proper partial pressures of the gases. After vigorous shaking for several minutes to facilitate equilibration, oxygen partial pressure was verified to be near 150 mmHg at one atmosphere. The external solution containing Xe was delivered *via* a peristaltic pump from an airtight glass syringe (50 ml), and data were recorded while exchanging solution to ensure control of the Xe concentration. The exchange time for extracellular solution (2–3 min) was based on attainment of steady-state effects.

**Recording Procedures and Data Analysis.** Current measurements were obtained using the whole-cell configuration of the patch clamp technique at room temperature. Pipettes were pulled from borosilicate glass (Garner, Claremont, CA) using a horizontal puller (Sutter Instruments, Novato, CA) and heat polished with a microforge (Narishige, Tokyo, Japan). Pipette resistances ranged from 1.8 to 2.3 M $\Omega$ . Current was measured with a List EPC-7 patch clamp amplifier (Adams & List Associates, Great Neck, NY) interfaced to a computer *via* a TL-1 Labmaster (Axon Instruments, Foster City, CA). The pClamp software (Version 6.0; Axon Instruments, Foster City, CA) was used for data acquisition and analysis.

The voltage protocol for  $I_{Na}$ ,  $I_{Ca,L}$ , and  $I_{Kir}$  were as follows:  $I_{Na}$  was recorded during 30-ms test pulses to +30 mV (10-mV increments) from a holding potential of -110 mV. For  $I_{Ca,L}$ , current was elicited by 50-ms test pulses to +50 mV (10-mV increments) from a holding potential of -50 mV.  $I_{Kir}$  was elicited by 50-ms test pulses to +50 mV (10-mV increments) from a holding potential of -40 mV.

#### Statistics

Data are expressed as means  $\pm$  SEM. Each isolated heart served as its own control. Responses to Xe were compared with the preceding controls by two-way anal-

ysis of variance in the intact heart studies. The effects of anesthetic concentrations on coronary flow and percent oxygen extraction during infusion of bradykinin were compared by Tukey comparison of means tests after analysis of variance for repeated measures (Super Anova 1.11 software for Macintosh; Abacus Concepts, Inc., Berkeley, CA). For the patch clamp studies, the number of cells studied in each experiment is denoted by *n*. Each cell served as its own control. Statistical significance in the patch clamp studies was evaluated using paired Student *t* test. Differences among means were considered statistically significant when  $P = 0.05$ .

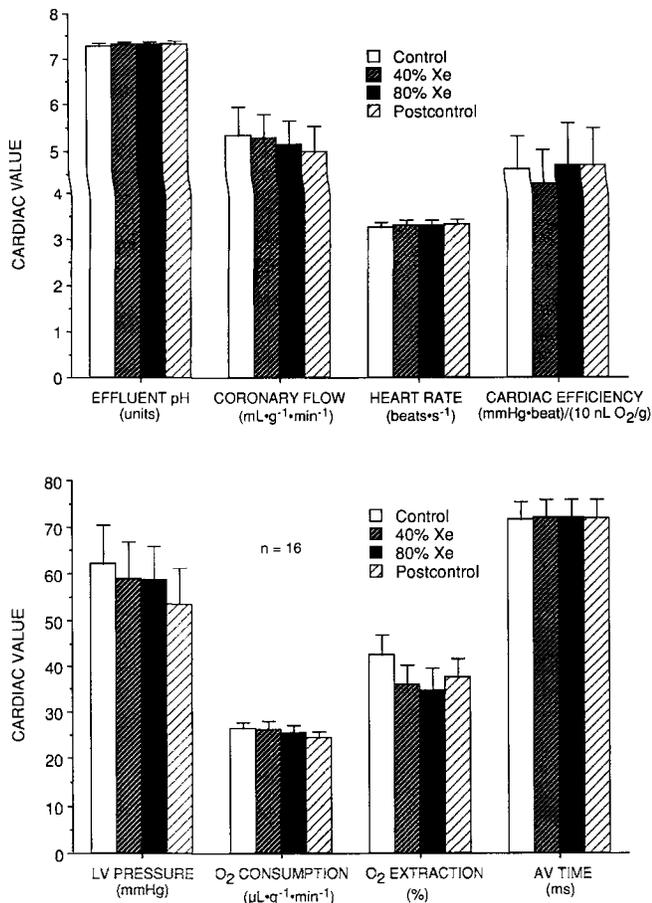
## Results

### Isolated Heart Studies

Figure 1 summarizes effects of exposure to Xe on eight measured or calculated variables in 16 isolated guinea pig hearts. Xe, 40% and 80%, did not alter the measured values of any variable from initial controls; post-Xe control values (postcontrol) were also not different from the initial controls. The lower LV pressure reflects the lower perfusate  $CaCl_2$  used in this study compared to our previous studies using crystalloid perfusate. Effluent values for coronary sinus oxygen tension and  $H^+$  concentration, respectively, were  $66 \pm 3$  mmHg and  $191 \pm 9$  nM (control),  $61 \pm 4$  mmHg and  $204 \pm 8$  nM (40% Xe),  $61 \pm 4$  mmHg and  $204 \pm 8$  nM (80% Xe), and  $61 \pm 5$  mmHg and  $208 \pm 10$  nM (postcontrol). These values were not different between Xe treatments and controls (control or postcontrol, 0% Xe). Figure 2 shows that bradykinin increased flow similarly in the presence and absence of 80% Xe. On return to Krebs-Ringer's perfusion, post-erythrocyte perfusion values were similar to preperfusion values.

### Patch Clamp Studies

The effects of 80% Xe on the cardiac  $I_{Na}$ ,  $I_{Kir}$ , and  $I_{Ca,L}$  currents in three myocytes are shown in figure 3. The superimposed current traces and corresponding current-voltage relationships indicate that Xe had no significant effects on the cardiac ionic currents measured. Figure 4 shows that current amplitude, measured at +10 mV for  $I_{Ca,L}$ , -20 mV for  $I_{Na}$ , and -110 mV for  $I_{Kir}$ , was not significantly altered by Xe:  $-2 \pm 3\%$  for  $I_{Ca,L}$  ( $n = 5$ ),  $-2 \pm 2\%$  for  $I_{Na}$  ( $n = 7$ ), and  $-4 \pm 3\%$  for  $I_{Kir}$  ( $n = 5$ ). These results are unlike the inhibitory effects on cardiac currents of halothane and sevoflurane at or above 1 MAC, as also shown in figure 4. These effects of halothane and sevoflurane on  $I_{Na}$  and sevoflurane on  $I_{Kir}$  have



**Fig. 1.** Lack of effect of two concentrations of xenon (Xe) dissolved in erythrocyte-Krebs-Ringer's solution on eight cardiac variables in guinea pig isolated hearts perfused at constant pressure. C = control before Xe; Postcontrol = last control after Xe; LV pressure = left ventricular isovolumetric pressure; AV = atrioventricular.

been previously reported by our laboratory.<sup>21,22</sup> Sevoflurane was tested at 3.0% on  $I_{Ca,L}$  ( $n = 7$ ), 2.0% on  $I_{Na}$  ( $n = 14$ ), and 2.6% on  $I_{Kir}$  ( $n = 5$ ). The concentrations of halothane on the corresponding ionic currents were 1.2% ( $n = 19$ ), 1.0% ( $n = 12$ ), and 2.0% ( $n = 7$ ), respectively.<sup>21,22</sup> At these anesthetic concentrations, sevoflurane and halothane significantly inhibited  $I_{Ca,L}$ ,  $I_{Na}$ , and  $I_{Kir}$ .

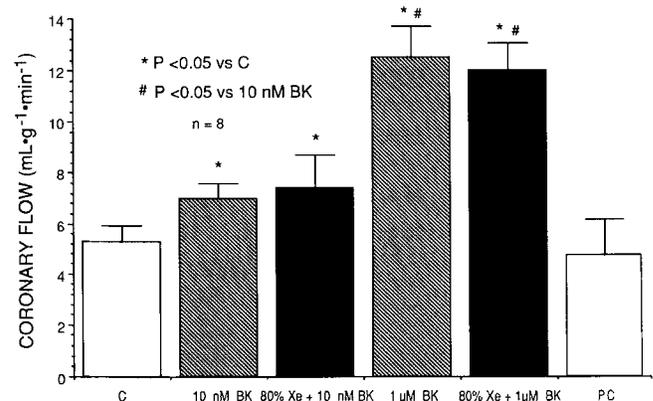
## Discussion

This is the first study to demonstrate that Xe has no obvious mechanical, electrical, or metabolic cardiac effects in intact, isolated perfused hearts or on  $I_{Ca,L}$ ,  $I_{Na}$ , and  $I_{Kir}$  currents in isolated cardiomyocytes of the guinea pig. Spe-

cifically, in the erythrocyte-Krebs-Ringer's perfused isolated heart, devoid of nervous or hormonal influences, Xe did not significantly alter heart rate, atrioventricular conduction time, coronary flow, or flow responses to bradykinin, isovolumetric LV pressure, percent oxygen extraction, myocardial oxygen consumption, or cardiac work efficiency. In isolated cardiac myocytes, Xe had no significant effect on the current voltage relationships of the three cardiac ion currents recorded,  $I_{Na}$ ,  $I_{Ca,L}$ , and  $I_{Kir}$ . Our results suggest that Xe, unlike volatile anesthetics at equivalent MAC,<sup>15-18</sup> has no, or very minimal, physiologically important effects on the heart.

Our findings agree generally with other studies in which the cardiovascular effects of Xe have been examined. Inhalation of Xe has been reported not to cause circulatory instability in pigs.<sup>25</sup> Xe produces minimal cardiovascular actions in the presence of isoflurane in dogs with and without experimental dilated cardiomyopathy.<sup>26</sup> In humans, Xe has also been found not to produce adverse effects.<sup>7-12</sup> Although Xe is only moderately more efficacious than  $N_2O$ , Xe has a rapid onset and offset of action and it is nonpolluting and nonmetabolized. Xe has a blood:gas partition coefficient of 0.14, which is significantly lower than those of other clinically used inhalational anesthetics,<sup>6</sup> and even lower than that of  $N_2O$  (0.47), sevoflurane (0.65), or desflurane (0.42), a property that predicts a more rapid onset of anesthesia and a more rapid emergence from anesthesia by Xe relative to all other commonly used anesthetics.<sup>11,12</sup>

Cellular membranes are regarded as the primary site for the complex action of anesthetics. Many studies have shown that both volatile and intravenous anesthetics exert



**Fig. 2.** Effects of bolus intraaortic injection of bradykinin (BK) on peak coronary flow in guinea pig hearts perfused with erythrocyte-Krebs-Ringer's solution in the presence and absence of xenon (Xe). Xe did not alter the coronary flow response to bradykinin.

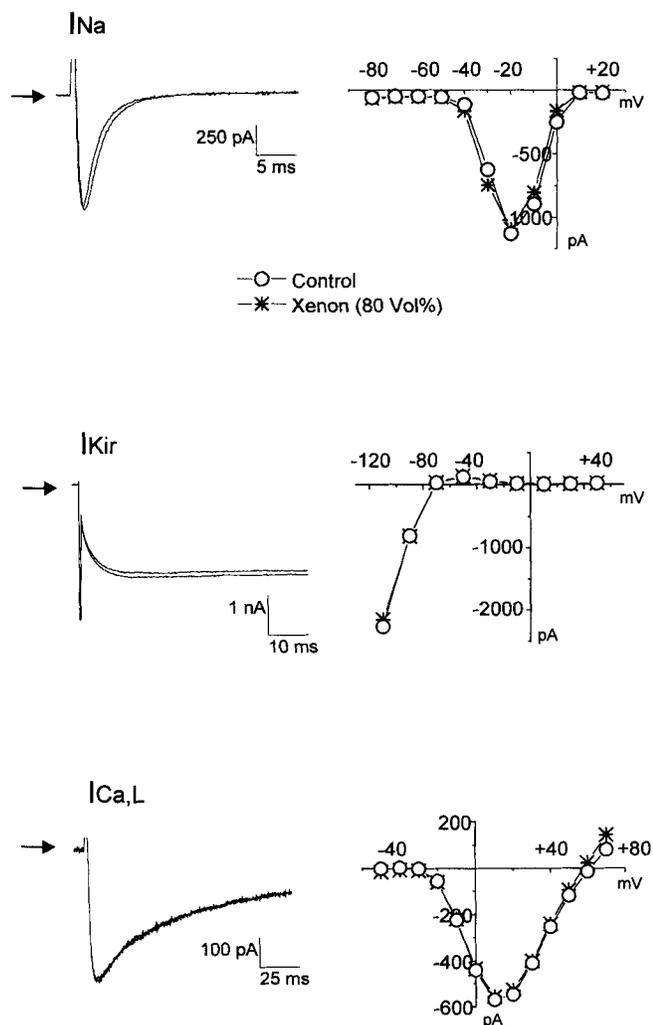


Fig. 3. Effects of 80 vol% Xe on cardiac ionic currents in single cardiac myocytes. (Left) Sample current traces recorded from three different myocytes were monitored at test potentials of  $-20$  mV for  $I_{Na}$ ,  $-110$  mV for  $I_{Kir}$ , and  $+10$  mV for  $I_{Ca,L}$ . Holding potentials were  $-110$  mV for  $I_{Na}$ ,  $-40$  mV for  $I_{Kir}$ , and  $-50$  mV for  $I_{Ca,L}$ . Arrows indicate zero-current levels. (Right) Corresponding current-voltage relationships for  $I_{Na}$ ,  $I_{Kir}$ , and  $I_{Ca,L}$  are shown.

potent—usually inhibitory—interaction with current flow through ion channels. Even among chemically similar anesthetics, mechanisms involved in ion current inhibition differ widely. For example, we have demonstrated that the volatile anesthetic halothane shows a conformational state-dependent effect on  $I_{Na}$ .<sup>23</sup> Furthermore, halothane affects  $I_{Na}$  by interference with G-protein-dependent and cyclic adenosine monophosphate-dependent pathways.<sup>24</sup> In the same studies, the chemically related volatile anesthetic isoflurane showed potent effects on  $I_{Na}$  as well, but the mechanisms of action were different as cyclic adenosine

monophosphate-dependent pathways were not affected. However, as a third volatile anesthetic, sevoflurane is characterized by unique effects on cardiac ion channels such as  $I_{Kir}$ .<sup>22</sup>

This is the first study to demonstrate that the gaseous anesthetic Xe has no obvious cardiac effects on the subcellular level, e.g., on ion channel protein function. The lack of direct myocardial and cardiomyocyte effects of Xe suggests that Xe has no effect on excitable muscle tissue, yet it has anesthetic activity on the nervous system. This may arise from a much lesser ion channel sensitivity of Xe for cardiac and smooth muscle cells than for neurons. The anesthetic mechanism of action of Xe remains to be determined, although some advances have been made recently.

Because Xe is uncharged and nonpolar in the gaseous state, the mechanism by which it produces anesthesia remains to be fully explained. The lack of effect of Xe compared with the commonly used anesthetics on cardiac myocyte currents and myocardial function suggests that anesthesia may not be necessarily mediated *via* alteration of ion channel protein binding or channel conformation. Trudell *et al.*<sup>27</sup> have modeled a binding site for Xe and other inert molecules in metmyoglobin in which the binding energy derived from hyperbaric gas experiments was matched to calculated binding energies that would result (1) from induction of a dipole in the Xe molecule by a charged binding site on metmyoglobin,

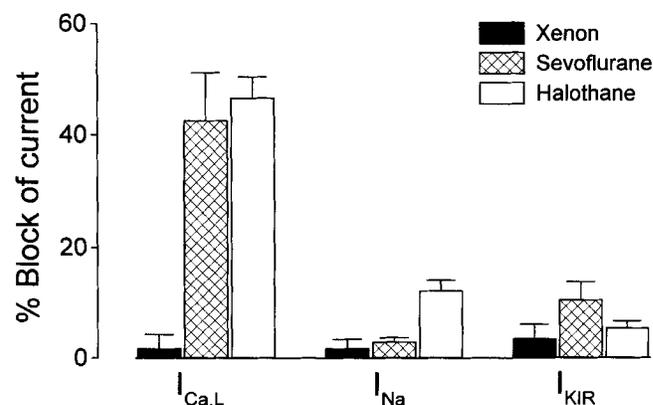


Fig. 4. Summary of the effects of three anesthetics on cardiac ionic currents. Percent block of current amplitude for  $I_{Ca,L}$ ,  $I_{Na}$ , and  $I_{Kir}$  were determined at test potentials displayed in figure 3 and described in the text. For  $I_{Ca,L}$  and  $I_{Na}$ , peak current amplitude was measured. For  $I_{Kir}$ , current amplitude was measured at the end of a 50-ms test pulse. The concentration of Xe was 80%. As published previously,<sup>21,22</sup> the concentrations of sevoflurane were 3.0% on  $I_{Ca,L}$ , 2.0% on  $I_{Na}$ , and 2.6% on  $I_{Kir}$ . The concentrations of halothane on the corresponding ionic currents were 1.2%, 1.0%, and 2.0%, respectively. Each concentration of halothane and sevoflurane, but not Xe, depressed the respective current.

and (2) from redistribution of electrons in a molecule that produces an instantaneous dipole in that molecule. They reported an association between theoretical and calculated binding energies and suggested that binding energies of inert gases can be used to predict anesthetic potency. However, the actual site of anesthetic action remains unknown.

The high cost of procuring Xe initially prevented its practical introduction into anesthesia practice. The recent development of a minimal total gas flow delivery and total rebreathing system may minimize the cost. The characteristic cardiovascular stability afforded by Xe in anesthesia may be beneficial for the patient with cardiac disease who cannot tolerate the depressant effects of the commonly used volatile anesthetics. With the advent of new scavenging techniques, Xe could emerge as a practical and very safe general anesthetic.

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