Xenon and nitrous oxide do not depress cardiac function in an isolated rat heart model

[Le xénon et le protoxyde d'azote ne diminuent pas la fonction cardiaque d'un cœur de rat isolé]

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Purpose: To examine the inotropic and chronotropic effects of xenon (Xe) and nitrous oxide (N_2O) compared with nitrogen (N_2) on isolated rat hearts. The differences between Xe and N_2O were also compared.

Methods: The effects of Xe, N_2O and N_2 on coronary perfusion pressure (CPP), heart rate, left ventricular developed pressure (LVDP) and double product (DP) were examined in isolated rat hearts perfused at constant flow (10 mL·min^{-1}). Following stabilization and baseline measurement with 95% O_2 (plus 5% CO_2), the heart was exposed to buffer equilibrated with one of three test gases; 50% N_2 with 45% O_2 (Group N_2: n=9), 50% Xe with 45% O_2 (Group Xe: n=9), or 50% N_2O with 45% O_2 (Group N_2O: n=9) for 30 min. Measurements were performed in the last minute of exposure to the test gases.

Results: Gas exposure in all three groups decreased O_2 delivery (-50%), CPP (-11%), LVDP (-30%) and DP (-44%) compared with baseline values (P <0.001). However, there were no differences among the groups.

Conclusion: Our data suggest that cardiac contractility was decreased by the effects of reduced O_2 delivery, but both Xe and N_2O did not cause further cardiac depressant effects compared to N_2 in this experimental model.

Objectif : *Vérifier les effets inotropiques et chronotropiques du xénon (Xe) et du protoxyde d'azote (N_2O) comparés à ceux de l'azote (N_2) sur des cœurs de rats isolés. Comparer aussi les différences entre le Xe et le N_2O.*

Méthode : *Les effets du Xe, de N_2O et de N_2 sur la pression de perfusion coronarienne (PPC), la fréquence cardiaque (FC) la pression développée dans le ventricule gauche (PDVG) et le double produit (DP) ont été vérifiés dans des cœurs de rat isolés perfusés à débit constant (10 mL·min^{-1}). Après la stabilisation et les mesures de base avec de l'O_2 à 95 % (plus du CO_2 à 5 %), le cœur a été exposé à un tampon équilibré avec l'un des trois gaz expérimentaux ; N_2 à 50 % avec O_2 à 45 % (Groupe N_2 : n = 9), Xe à 50 % avec O_2 à 45 % (Groupe Xe : n = 9) ou N_2O à 50 % avec O_2 à 45 % (Groupe N_2O : n = 9) pendant 30 min. Les mesures ont été faites pendant la dernière minute de l'exposition aux gaz testés.*

Résultats : *Dans les trois groupes, l'exposition aux gaz a réduit l'apport d'O_2 (-50 %), la PPC (-11 %), la PDVG (-30 %) et le DP (-44 %) par rapport aux mesures initiales (P < 0,001). Il n'y a cependant pas eu de différence intergroupe.*

Conclusion : *Nos données laissent croire que la contractilité cardiaque a été abaissée par les effets d'un apport réduit d'O_2, mais que ni le Xe ni le N_2O comparés au N_2 n'ont causé de dépression cardiaque supplémentaire chez ce modèle expérimental.*

XENON (Xe) has many of the properties of an ideal anesthetic, because it is non-explosive, non-toxic, non-teratogenic, and probably is not metabolized.[1–3] Xe also offers rapid induction and recovery from anesthesia[4,5] due to its extremely low blood/gas partition coefficient (0.115–0.14).[6,7] The minimum alveolar concentration (MAC) of Xe is 71% in humans, indicating that it is a moderately more potent anesthetic than nitrous oxide (N_2O) (104%).[6,8] In these respects, Xe has been proposed as a replacement for N_2O in clinical use.[4,9] However, the direct and global effects of Xe on the heart have not been compared with those of N_2O.

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The current investigation examined the action of Xe compared with N_2O and nitrogen (N_2) in isolated rat hearts using the Langendorff preparation to avoid the mechanical, humoral and autonomic nervous system influences of Xe.

We tested the hypothesis that 50% Xe does not produce inotropic or chronotropic adverse effects compared with the effects of N_2O on isolated rat hearts.

Materials and methods

Langendorff heart preparation

The study protocol was approved by the Institutional Animal Care Committee of the University of Tsukuba. Twenty seven male Sprague-Dawley rats (weighing 380–460 g, aged 13–14 weeks) were injected *ip* with 35 mg (76–92 mg·kg^{-1}) sodium pentobarbitone and 1,000 units heparin. Following thoracotomy, the heart was rapidly excised and perfused *via* retrograde cannulation of the aorta in a Langendorff apparatus at a constant flow of 10 mL·min^{-1} (Radnoti Grass®; Monrovia, CA, USA) using modified Krebs-Henseleit (K-H) buffer.[10] K-H buffer was composed of (mM) NaCl 118, KCl 4.7, KH_2PO 1.2, $MgSO_4$ 1.2, $CaCl_2$ 2.8, $NaHCO_3$ 25, glucose 5.5 and sodium pyruvate 2.0. Constant flow was maintained throughout the experiment. Buffer and bath temperatures were maintained at 37.5 ± 0.3°C throughout the experiment with a thermostatically controlled recirculating water bath (Harvard Thermocirculator®, Kent, UK).

Systolic left ventricular pressure was measured isovolumetrically with a transducer connected to a thin, saline-filled, latex balloon. The balloon was inserted into the left ventricle through the mitral valve *via* an incision in the left atrium. Balloon volume was adjusted to create an end-diastolic left ventricular pressure of 0 or less than 5 mmHg during the initial baseline period. The volume of the balloon was not modified until the end of the experiment. Spontaneous heart rate (HR) was determined from the left ventricular contraction interval. Left ventricular developed pressure (LVDP) was calculated by subtracting end-diastolic left ventricular pressure from left ventricular peak systolic pressure, which was regarded as an index of contractile function of the isolated heart. Double product (DP) was calculated as follows: HR × LVDP/1000, which is an estimate of myocardial oxygen demand. Coronary perfusion pressure (CPP), which reflects coronary artery resistance, was measured by a pressure transducer (TruWave™ UK0804SA, Edwards, Inc., CA, USA) connected to the aortic cannula, the tip of which was positioned just above the aortic valve. Isovolumetric left ventricular pressure, spontaneous HR and CPP were measured continuously (M1166A Model 66S, Hewlett Packard Co. Ltd., Boeblingen, Germany). Oxygen delivery (DO_2) was calculated from the inflow O_2 tension × O_2 solubility (0.0031 mL·mmHg^{-1}·100 mL^{-1}) × coronary flow per gram wet heart tissue.[11] Oxygen extraction ratio was calculated as follows: (inflow O_2 content - outflow O_2 content) × 100 / inflow O_2 content.

Protocol

Before the experiment, four cylinders containing 95% O_2 + 5% CO_2, 50% N_2 + 45% O_2 + 5% CO_2, 50% Xe + 45% O_2 + 5% CO_2, and 50% N_2O + 45% O_2 + 5% CO_2

TABLE I Inflow pH, PCO_2, PO_2 and calculated DO_2

	Group N_2 (n=9)		*Group Xe (n=9)*		*Group N_2O (n=9)*	
	95% O_2	*50% N_2*	*95% O_2*	*50% xenon*	*95% O_2*	*50% nitrous oxide*
pH	7.44 ± 0.02	7.45 ± 0.03	7.44 ± 0.02	7.45 ± 0.02	7.43 ± 0.03	7.44 ± 0.03
PCO_2 (mmHg)	34 ± 3	33 ± 2	34 ± 2	33 ± 1	33 ± 3	32 ± 3
PO_2 (mmHg)	573 ± 11	285 ± 8*	577 ± 7	288 ± 11*	591 ± 12	297 ±9*
DO_2 (μL·g^{-1}·min^{-1})	131 ± 4	65 ± 2*	130 ± 4	66 ± 2*	131 ± 6	66 ± 3*

Data are mean ± SEM. DO_2=oxygen delivery; PCO_2=carbon dioxide tension; PO_2=oxygen tension. *P <0.05 *vs* baseline (95% O_2).

TABLE II Cardiac variables in the three groups

	Group N_2 (n=9)		*Group Xe (n=9)*		*Group N_2O (n=9)*	
	95% O_2	*50% N_2*	*95% O_2*	*50% xenon*	*95% O_2*	*50% nitrous oxide*
CPP (mmHg)	44 ± 1	38 ± 1*	46 ± 1	40 ± 1*	42 ± 1	38 ± 2*
HR (beats·min^{-1})	249 ± 4	223 ± 9	252 ± 6	215 ± 9	248 ± 7	224 ± 12
LVDP (mmHg)	102 ± 3	70 ± 3*	98 ± 3	66 ± 3*	108 ± 5	73 ± 4*
DP (mmHg x 1000·min^{-1})	25 ± 1	15 ± 1*	25 ± 1	14 ± 1*	27 ± 1	16 ± 1*

Data are mean ± SEM. CPP=coronary perfusion pressure; HR=heart rate; LVDP=left ventricular developed pressure; DP=double product. *P <0.05 *vs* baseline (95% O_2).

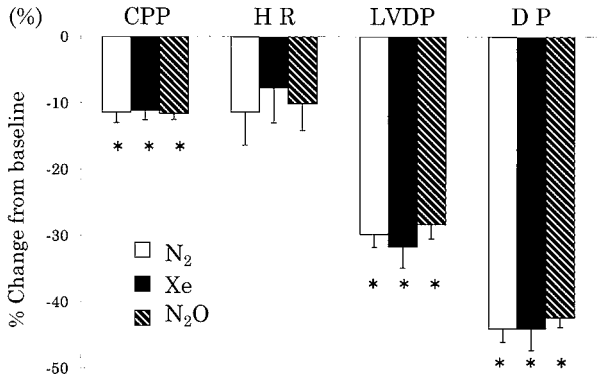

FIGURE Percent change of cardiac variables from baseline. There were no differences in % change of cardiac variables between groups N_2, Xe and N_2O. CPP=coronary perfusion pressure; HR=heart rate; LVDP=left ventricular developed pressure; DP=double product. *P <0.05 *vs* baseline.

were prepared. The concentration of each gas in the cylinders was measured by gas chromatography. After 30 min of perfusion with buffer for equilibration with 95% O_2 and 5% CO_2, baseline measurements were taken. The hearts were then randomly assigned to one of three groups. In Group N_2 (n=9), the hearts were exposed to buffer equilibrated with 50% N_2, 45% O_2 and 5% CO_2. In Group Xe (n=9), the hearts were exposed to buffer equilibrated with 50% Xe, 45% O_2 and 5% CO_2. In Group N_2O (n=9), the hearts were exposed to buffer equilibrated with 50% N_2O, 45% O_2 and 5% CO_2. After a 30-min period of exposure to buffer with test gases, measurements were made.

Statistics

All data are expressed as mean ± SEM. Statistical analysis was performed on a personal computer with the statistical package SPSS® for Windows (available software package SPSS® for Windows 9.0.1 J). Variables were analyzed twice: by paired t test to analyze change from baseline, and by ANOVA to analyze between group differences. P values of less than 0.05 were considered significant.

Results

Inflow pH and carbon dioxide tension (PCO_2) were identical in the three groups. Oxygen tension (PO_2) and calculated DO_2 decreased in the three groups after exposure to buffer equilibrated with test gases. However, there were no statistically significant differences among the three groups (Table I).

CPP, LVDP and DP were decreased by exposure to buffer equilibrated with test gases. However, these variables were not different among the three groups (Table II).

Percent changes of CPP, LVDP and DP from baseline decreased in all three groups. However, these changes were not different among the groups (Figure).

Oxygen extraction ratio decreased significantly (P <0.001) with exposure to Xe (-28 ± 6%), N_2O (-25 ± 2%) and N_2 (-27 ± 4%) compared with 95% O_2. However, there were no differences between the three groups.

Discussion

In the present study, the administration of Xe, as well as N_2O, produced cardiodepressant effects in isolated rat hearts; however, these were identical to the effects of N_2. This means that the cardiodepressant effects observed with Xe and N_2O were due to reduced oxygen delivery, and that Xe or N_2O themselves did not have cardiodepressant effects.

Previously, many studies have surmised that Xe causes minimal cardiovascular effects. Xe produced little effects on hemodynamics in pigs,[12] and minimal cardiovascular effects were observed in dogs with and without experimental dilated cardiomyopathy during Xe inhalation.[13] The latter finding indirectly suggested that Xe may be tolerated in unfavourable conditions, i.e., preexisting LV dysfunction. Xe has been shown not to alter voltage-gated ion channels in the myocardium,[14] nor does it sensitize the myocardium to the dysrhythmogenic effects of epinephrine.[15] In humans, Xe was also found to provide stable cardiovascular conditions.[2,5,16] Stowe *et al.* reported that Xe displayed no, or very minimal, physiologically important effects on isolated erythrocyte-perfused guinea pig hearts.[17] Our results are consistent with these findings in that, regarding cardiac depressant effects, Xe exhibited no difference relative to N_2 in isolated rat hearts.

Several studies have suggested that Xe might cause a decrease in HR,[3,16,18,19] despite reports of little effect on hemodynamics in *in vivo* studies. The current investigation examined the effects of Xe in isolated rat hearts with Langendorff perfusion to avoid mechanical, humoral, and autonomic nervous system influences of the gas. Our results show that isolated hearts maintained a stable spontaneous HR during exposure to Xe. Xe was reported to depress both sympathetic and parasympathetic transmission more than isoflurane at 0.8 MAC, and was suggested to be relatively vagotonic in clinical trials.[20] Further, the HR response can vary with autonomic tone and baroreflex activation.[21] Therefore, the decrease in HR with Xe *in vivo* may be

mediated *via* the cardiac autonomic nervous system. Xe is also capable of preventing activation of the adrenal medullary system[3] and inhibits adrenal secretion,[3,12] which might result in decreased HR *in vivo*.

Many years of clinical experience with N_2O indicate that it possesses mild cardiovascular depressant effects that may be counterbalanced by a simultaneous, reflexly mediated increase in sympathetic tone. These studies demonstrated small increases,[22] small decreases,[23] or no change[24] in indices of contractility. A few *in vitro* investigations regarding the effects of N_2O on myocardial muscle have indicated that N_2O depressed contractility similar to, or more than that in controls.[25–27] Regarding sympathetic effects, N_2O, but not Xe, has been reported to augment its outflow. The sympathetic activation by N_2O has been shown by elevated plasma catecholamine concentrations[23] and by microneurography.[28,29] This sympatho-activating property of N_2O can complicate evaluation of its cardiovascular effects and direct effects on cardiac function. In an isolated global heart study, Stowe *et al.* reported that N_2O caused only small but significant depression of indices of cardiac contractility.[11] Our findings, however, showed that 50% N_2O produced no cardiodepressant effects compared with an identical concentration of N_2, which is inconsistent with their report.[11] No statistically significant difference between Xe, N_2O and N_2, could be shown but N_2O tended to be cardiodepressant. The number of hearts studied in the current laboratory investigation may not have been sufficient to confirm the cardiodepressant effects of N_2O. Meanwhile, Xe did not depress cardiac function more than N_2O, at least in the absence of autonomic influence or changes in preload and afterload.

The effect of the restriction of O_2 delivery is a limitation of the current investigation. The hearts were solely dependent on the crystalloid solution from which to extract dissolved O_2. Exposure to 50% Xe (i.e., exposure to 45% O_2) decreased O_2 delivery with, possibly, a consequent mild hypoxic condition in isolated hearts[11] (Table I). Even under such conditions, however, Xe produced identical changes in CPP, LVDP and DP compared with N_2.

As mentioned initially, Xe surpasses N_2O in several points; lower blood/gas partition coefficient (0.115–0.14),[6,7] higher MAC (71% in humans),[6,8] and innocuousness to the environment, because Xe is prepared by fractional distillation of atmospheric air. Therefore, the replacement of N_2O with Xe may become appropriate when delivery systems (i.e., closed circuit) become available with efficient techniques for recycling the gas to decrease the cost of Xe anesthesia.[30]

In conclusion, 50% Xe produced cardiac effects identical to those of N_2O or N_2 in isolated rat hearts under conditions of decreased O_2 delivery. Xe itself lacks cardiodepressant effects and may become a useful alternative to N_2O.

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