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Cardiovascular effects of xenon and nitrous oxide in patients during fentanyl-midazolam anaesthesia*

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Summary

Xenon anaesthesia appears to have minimal haemodynamic effects. The purpose of this randomised prospective study was to compare the cardiovascular effects of xenon and nitrous oxide in patients with known ischaemic heart disease. In 20 patients who were due to undergo coronary artery bypass graft surgery, 30 min following induction of anaesthesia with fentanyl 30 $\mu g.kg^{-1}$ and midazolam 0.1 $mg.kg^{-1}$ but prior to the start of surgery, xenon or nitrous oxide 60% was administered for 15 min. The results showed that xenon caused a minimal decrease in the mean arterial pressure (from 81 (7) to 75 (8) mmHg, mean (SD)), but did not affect the systolic function of the left ventricle, as demonstrated by unchanged left ventricular stroke work index (LVSWI) and the fractional area change of the left ventricle (FAC) derived from transoesophageal echocardiography (TOE). However, in contrast, nitrous oxide was found to decrease the mean arterial pressure (from 81 (8) to 69 (7) mmHg), the LVSWI, and the FAC. The cardiac index, central venous and pulmonary artery occlusion pressures, systemic and pulmonary vascular resistances, and the TOE-derived E/A ratio through the mitral valve were unchanged by xenon or nitrous oxide. We conclude that xenon provides improved haemodynamic stability compared with nitrous oxide, conserving the left ventricular systolic function.

Keywords *Anaesthetics*, inhalational; inert gases. *Cardiac function*. *Transoesophageal echocardiography*.

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The inert gas xenon has been attracting renewed interest because it possesses many of the properties of an ideal anaesthetic agent [1]. The first multicentre clinical trial has been completed recently, and the results have demonstrated that xenon provides anaesthesia as effectively and safely as does nitrous oxide (N_2O)-isoflurane anaesthesia. Xenon provided more rapid recovery from anaesthesia [2].

Xenon appears to provide haemodynamic stability in healthy humans [2–4] and in animals with compromised myocardial function [5,6], at least in part by preserving cardiac contractility [7,8]. However, there have only been three human studies that have closely examined the cardiovascular effects of xenon using modern monitoring devices such as a pulmonary artery catheter or transoesophageal echocardiography (TOE). One study was performed in healthy surgical patients [3]. In two other studies performed by the same investigators [9,10], xenon was used at an average concentration of only 27–28%

to produce sedation but not anaesthesia (the minimum alveolar concentration [MAC] of xenon is 71% [11]). To the best of our knowledge, no studies have examined the effects of anaesthetic concentrations of xenon in patients with known cardiac disease. Because previous studies have revealed minimal cardiovascular effects of xenon [3,9,10], we hypothesised that xenon at an anaesthetic concentration would provide haemodynamic stability in patients with ischaemic heart disease. Therefore, we compared the haemodynamic effects of 60% xenon and N_2O using a TOE and a pulmonary artery catheter in patients due to undergo coronary artery bypass graft (CABG) surgery.

Patients and methods

Patients

This study was approved by the Ethics Committee of Teikyo University School of Medicine. After obtaining written informed consent, we studied 20 patients (age 47–76 years) scheduled for elective CABG. The exclusion criteria included the presence of congestive heart failure, chest pain in the 3 days prior to surgery, the need for continuous intravenous (i.v.) infusion of heparin, anti-anginal drugs, or vasoactive drugs (e.g. nitroglycerin, diltiazem, nicorandil and dopamine), and the presence of significant pulmonary diseases. The final criterion was added because, during administration of 60% xenon or nitrous oxide, the patient has to tolerate an inspired oxygen concentration of 40% or less.

All patients were receiving an antiplatelet drug (mostly aspirin) and isosorbide dinitrate, and all but two patients were taking a calcium antagonist (diltiazem or nifedipine). At randomisation (see below), one patient who was not receiving a calcium antagonist was allocated to receive xenon and the other to receive N_2O. Only one patient was taking a beta-blocking agent (propranolol) because Japanese cardiologists rarely prescribe beta-blockers; at randomisation, this patient was assigned to receive xenon.

Protocol

All patients received their anti-anginal and other chronic medications until the morning of surgery, unless otherwise instructed by the cardiac surgical team. Anaesthetic premedication consisted of morphine 0.1 $mg.kg^{-1}$ and scopolamine 5 $\mu g.kg^{-1}$ given intramuscularly 1 h prior to arrival to the operating theatre. In the operating theatre, i.v. and radial arterial lines were placed under local anaesthesia, and routine monitoring, including two-lead ECG (II and V_5 leads), was commenced. General anaesthesia was then induced using fentanyl 30 $\mu g.kg^{-1}$ and midazolam 0.1 $mg.kg^{-1}$ i.v. The trachea was intubated following the administration of vecuronium 20 mg i.v., and the lungs were ventilated using 100% oxygen. No volatile anaesthetics were administered. A pulmonary artery catheter (Swan-Ganz CCO, Baxter, Irvine, CA, USA) was placed and connected to a continuous cardiac output monitor (Vigilance, Baxter). A 5.0 MHz ultrasound transducer (21364 A, Hewlett Packard, Palo Alto, CA, USA) was introduced into the oesophagus and connected to an imaging system (77035 A, Hewlett Packard). The patients were then left unstimulated until the end of the study period except for prepping and draping.

The patients were randomly allocated to receive either xenon ($n = 10$) or N_2O ($n = 10$). The baseline haemodynamic parameters and the TOE data were obtained 30 min after tracheal intubation. The assigned anaesthetic then was administered using a VIP 100 anaesthesia machine (IMI, Saitama, Japan) initially at a high flow rate (3 $l.min^{-1}$) combined with oxygen (1 $l.min^{-1}$). In the xenon patients, once the end-tidal concentration of xenon reached 60%, the flows of xenon and oxygen were reduced and the breathing circuit was closed to minimise the waste of xenon. (Xenon costs approximately US $10 per litre.) In the N_2O patients, N_2O 1.5 $l.min^{-1}$ and oxygen 1 $l.min^{-1}$ were administered using the semiclosed breathing system. After the end-tidal concentrations of xenon and N_2O had been maintained at 60% for 15 min, the second haemodynamic and TOE measurements were performed. Xenon and N_2O were then discontinued and the patient's lungs were again ventilated with 100% oxygen using a flow rate of 6 $l.min^{-1}$. The third (postinhalation) measurements were performed 10 min later. The patients received no anaesthetics or medications other than those listed above. Subsequent anaesthesia was left to the discretion of the anaesthetist, and the surgery was allowed to begin.

The protocol called for immediate termination of the study if the systolic blood pressure was < 90 mmHg or new changes in the ECG occurred, consistent with or suggestive of myocardial ischaemia. In such cases, inhalational anaesthetics were discontinued and appropriate supportive measures were initiated at the discretion of the anaesthetist.

The end-tidal concentrations of N_2O and carbon dioxide were continuously monitored using a Dräger PM8050 gas monitor (Dräger, Lübeck, Germany). The end-tidal concentration of xenon was continuously monitored using a xenon analyser (Anzai Medical, Tokyo, Japan), whose effective working range is 1–100% with a $\pm$ 1% error and a 90% response time of less than 1 s. These analysers were calibrated before each use according to the manufacturers' instructions.

Transoesophageal echocardiography

A single designated investigator (Y.N.) who was blinded to the inhalational anaesthetic administered performed

the TOE. The fractional area change (FAC) of the left ventricle in the short axis view at the mid-papillary level was calculated as an indicator of systolic left ventricular function according to the formula:

$$FAC = (EDA - ESA)/EDA$$

where EDA and ESA are end-diastolic and end-systolic areas of the left ventricle, respectively. In addition, the blood flow velocity through the mitral valve was measured in the four-chamber view, and the ratio of the E-wave over the A-wave velocity (E/A ratio) was calculated as an indicator of diastolic left ventricular function. Both the FAC and E/A ratio were reported as the mean of three consecutive heartbeats.

Pharmacokinetic calculations

The plasma concentrations of fentanyl and midazolam at each time point were estimated using Stanpump software (obtained by courtesy of Steven L. Shafer, M.D., Professor, Department of Anaesthesia, Stanford University, School of Medicine, Stanford, CA, USA) based on the parameters of McClain & Hug for fentanyl [12] and Greenblatt for midazolam [13].

Statistical analysis

Results are reported as mean (SD). For each haemodynamic or TOE parameter, the values at two of the three different time points within the same anaesthetic group were compared using paired *t*-tests, and the values of xenon and N_2O groups at the same time point were compared using unpaired *t*-tests. The statistical significance of these *t*-tests was judged using the modified Bonferroni correction for multiple comparisons. A p-value < 0.05 was considered statistically significant.

Results

The patients' demographics (Table 1) and the calculated plasma concentrations of fentanyl and midazolam (Table 2) were similar in the xenon and N_2O groups.

The haemodynamic and TOE parameters are presented in Table 3 and Fig. 1(A,B).

Table 1 Patient demographics.

	Xenon (n = 10)	N_2O (n = 10)
Age; years	63 (8), [49–76]	60 (10), [47–76]
Body weight; kg	58 (10)	62 (12)
Height; cm	158 (7)	156 (8)
Gender; M : F	8 : 2	6 : 4

N_2O; nitrous oxide.
Values are given as mean (SD), [range].

Table 2 Plasma concentrations of fentanyl and midazolam based on pharmacokinetic calculations.

	Baseline	During inhalation of xenon or N_2O	Postinhalation
Fentanyl; ng·ml^{-1}			
Xenon	5.4 (1.0)	4.5 (0.9)	4.2 (0.8)
N_2O	5.8 (1.1)	4.9 (0.9)	4.5 (0.9)
Midazolam; ng·ml^{-1}			
Xenon	36 (0.5)	29 (0)	27 (0)
N_2O	36 (0.4)	29 (0)	27 (0)

N_2O, nitrous oxide.

Table 3 Haemodynamic and echocardiographycally obtained parameters before (baseline), during and after inhalation of xenon or nitrous oxide (N_2O).

	Baseline	During inhalation of xenon or N_2O	Postinhalation
Mean arterial pressure; mmHg			
Xenon	81 (7)	75 (8)§	79 (8)
N_2O	81 (8)	69 (7)*§	78 (7)
Heart rate; beats·min^{-1}			
Xenon	66 (8)	60 (6)*	62 (7)*
N_2O	61 (6)	60 (6)	58 (5)
Central venous pressure; mmHg			
Xenon	7 (2)	7 (2)	7 (2)
N_2O	7 (3)	8 (3)	8 (3)
Pulmonary artery occlusion pressure; mmHg			
Xenon	8 (2)	8 (3)	8 (2)
N_2O	9 (3)	10 (3)	9 (3)
Cardiac index; l·min^{-1}·m^{-2}			
Xenon	2.3 (0.4)	2.2 (0.5)	2.2 (0.6)
N_2O	2.0 (0.5)	1.8 (0.4)	1.9 (0.4)
Systemic vascular resistance; dyn·s^{-1}·cm^{-5}			
Xenon	1726 (379)	1673 (458)	1790 (571)
N_2O	1901 (411)	1721 (332)	1948 (475)
Pulmonary vascular resistance; dyn·s^{-1}·cm^{-5}			
Xenon	147 (60)	162 (90)	163 (97)
N_2O	165 (53)	195 (63)	170 (60)
LVSWI; g·m^{-1}·beat·m^{-2}			
Xenon	34 (6)	32 (6)	34 (9)
N_2O	33 (7)	25 (5)*§¶	30 (6)
FAC; %			
Xenon	50 (17)	48 (8)	50 (14)
N_2O	46 (9)	36 (8)* §¶	46 (6)
E/A-ratio			
Xenon	0.9 (0.2)	1.0 (0.3)	1.0 (0.2)
N_2O	1.3 (0.7)	1.4 (0.6)	1.4 (0.5)

*p < 0.05 vs. baseline. §p < 0.05 vs. postinhalation. ¶p < 0.05 vs. xenon.
Values are given as mean (SD).
LVSWI, left ventricular stroke work index. FAC, fractional area change of the left ventricle in the short-axis view by the transoesophageal echocardiography (TOE). E/A ratio, the blood velocity ratio of the mitral valve E and A waves obtained by the TOE.

Generally, they remained unchanged during administration of xenon or N_2O, with the exceptions of the mean arterial pressure, the left ventricular stroke work

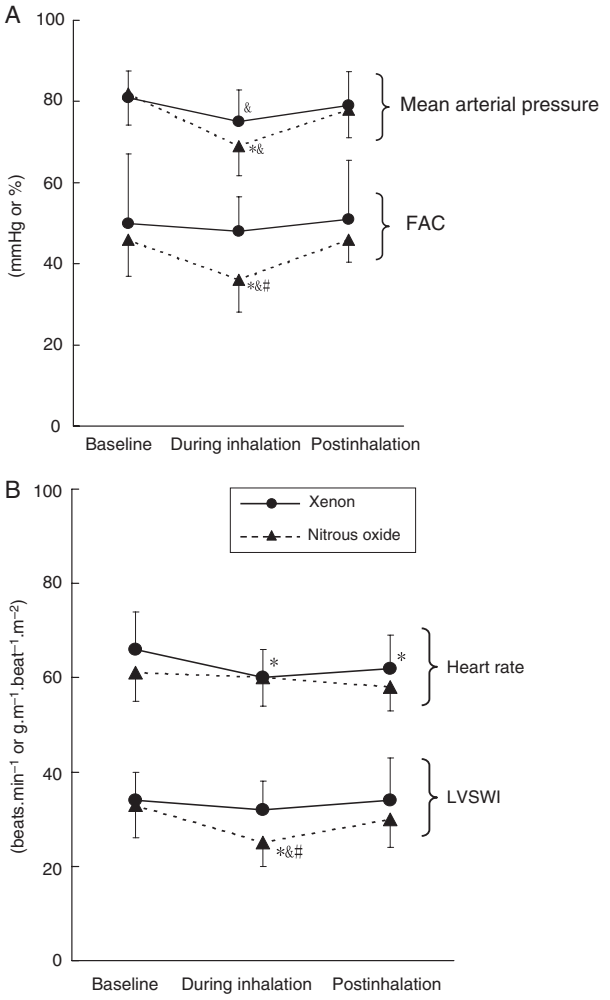

Figure 1 The mean arterial pressure, the fractional area change of the left ventricle (FAC) derived from transoesophageal echocardiography (Fig. 1A), the heart rate, and the left ventricular stroke work index (LVSWI; Fig. 1B) before (baseline), during, and after inhalation of xenon or nitrous oxide. *$p < 0.05$ vs. baseline. &$p < 0.05$ vs. postinhalation. #$p < 0.05$ vs. xenon.

index (LVSWI), the FAC, and the heart rate. The mean arterial pressure decreased by 6(6) mmHg from the baseline during xenon anaesthesia (nonsignificant, NS), and recovered to the baseline value after xenon was discontinued ($p = 0.0042$, during vs. post inhalation) (Fig. 1A). N_2O produced a highly significant decrease in the mean arterial pressure from the baseline (12(4) mmHg; $p < 0.0001$) that resolved following discontinuation of N_2O ($p = 0.0004$ during vs. post inhalation). LVSWI decreased during N_2O administration ($p = 0.0008$ baseline vs. during inhalation) and recovered after N_2O was discontinued ($p < 0.0001$, during vs. post inhalation; Fig. 1B). It remained unchanged during xenon administration. The LVSWI during N_2O administration was significantly lower than that during xenon administration ($p = 0.0071$). The FAC, which reflects the left ventricular systolic function, as does LVSWI, changed similarly (Fig. 1A). Xenon did not affect the FAC, whereas it was significantly reduced with N_2O compared to the baseline ($p = 0.0054$) or postinhalation ($p < 0.0001$). The FAC during N_2O administration was lower than that during xenon administration ($p = 0.0052$).

The heart rate decreased during xenon administration compared to the baseline ($p = 0.0032$ Fig. 1B). However, even after xenon was discontinued, it remained low compared to the baseline ($p = 0.0048$, baseline vs. post xenon inhalation). N_2O, on the other hand, had no effect on the heart rate.

All 20 patients successfully completed the study. Patients were specifically questioned postoperatively regarding recall; they were asked what was the last thing they remembered before they were anaesthetised and the first thing they remembered when they woke up, and if they remembered anything in between. We found no evidence of any recall in any patient.

Discussion

We have demonstrated that 60% xenon in oxygen can be administered safely with a degree of haemodynamic stability that was at least as good as that provided by N_2O in cardiac surgical patients during fentanyl-midazolam anaesthesia. Xenon slightly decreased the mean arterial pressure and the heart rate, but did not affect the systolic function of the left ventricle, as demonstrated by unchanged cardiac index, LVSWI and FAC. The central venous and pulmonary artery occlusion pressures, and the systemic vascular and pulmonary artery resistances remained unchanged, suggesting that xenon does not produce significant vasodilation.

The minimal cardiovascular effects of xenon we observed are consistent with previous findings in experimental models such as isolated perfused hearts [7,8], dogs with overpacing-induced cardiomyopathy [5], and rabbits with coronary artery ligation-induced left ventricular dysfunction [6]. It has been suggested that the underlying mechanism is the slight or nonexistent electrophysiological action of xenon on the important cation channels, including sodium, L-type calcium, and inward-rectifier and outward voltage-gated potassium channels [7,14].

Our results confirm that N_2O moderately decreases the mean arterial pressure and the left ventricular systolic function. This cardiac depressant action of N_2O has been previously well documented both clinically [15] and experimentally [16], and is thought to be due to a

decrease in the transsarcolemmal calcium influx, resulting in reduced availability of calcium within the myocardium [17].

Nitrous oxide stimulates the sympathetic nervous system [18], and it has been suggested that this action may counteract the direct myocardial depression it causes [16]. Xenon does not stimulate the sympathetic nervous system but is relatively vagotonic [19]. Therefore, sympathetic stimulation cannot explain the observed haemodynamic stability found during xenon anaesthesia.

Some [3,4], but not all [2], human studies have reported a tendency towards bradycardia during xenon anaesthesia. In our results, the heart rate decreased during xenon administration when compared to baseline values, and this persisted after xenon administration was discontinued. The difference between the values during and after xenon administration did not reach statistical significance. Therefore, it remains unclear how much of the observed reduction in the heart rate between the baseline and during administration of xenon is produced by xenon itself.

There are some limitations to the current study. First, we administered both fentanyl and midazolam as a single bolus dose on induction of anaesthesia instead of continuously infusing them to produce steady plasma concentrations. The pharmacokinetic calculations demonstrated that the plasma concentrations of fentanyl and midazolam decreased by approximately 20% over the 25-min study period (Table 2). However, it seems unlikely that this markedly confounded the results because the haemodynamic and TOE parameters, except for the heart rate in the xenon group, were not significantly different between the baseline and the postinhalation period.

The second limitation may be related to the use of MAC-fractions of xenon and N_2O that were not equivalent. Although xenon has a lower MAC than N_2O, both anaesthetics were administered at the same concentration of 60%. This was because we wished to test as high a concentration of xenon as clinically feasible. In our results, the cardiovascular effects of xenon were equivalent or less pronounced than those of N_2O. Therefore, any difference between the two anaesthetics we identified would have been greater had we used them at an equivalent MAC-fraction.

Our results have implications both clinically and scientifically. Clinically, xenon appears to be an attractive agent for patients with heart disease. Not only does it produce less haemodynamic depression than the conventional anaesthetics, but it is better at preventing haemodynamic and catecholamine responses to surgical stimuli than the volatile anaesthetics or N_2O because of its analgesic properties [20,21]. Moreover, xenon is a good hypnotic [22,23], and may reduce the risk of intraoperative awareness in such patients. Scientifically, the mechanisms by which a simple, inert molecule of xenon exerts many actions important for anaesthesia (amnesia, analgesia, and a lack of cardiac depression) are largely unknown. Further understanding of the mechanisms of xenon anaesthesia may facilitate the development of an 'ideal' anaesthetic that is more economically viable than xenon.

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