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Feasibility and Safety of Delivering Xenon to Patients Undergoing Coronary Artery Bypass Graft Surgery While on Cardiopulmonary Bypass

Phase I Study

Geoffrey G. Lockwood, M.B. B.S., Ph.D., Nicholas P. Franks, Ph.D., F.Med.Sci.,† Neil A. Downie, Ph.D.,‡ Kenneth M. Taylor, Ph.D., M.D., F.R.C.S., F.R.C.S.E., § Mervyn Maze, M.B., Ch.B., F.R.C.P., F.R.C.A., F.Med.Sci.‖*

Background: **Postoperative neurocognitive deficit is prevalent after cardiac surgery. Xenon may prevent or ameliorate acute neuronal injury, but it also may aggravate injury during cardiac surgery by increasing bubble embolism. Before embarking on a randomized clinical trial to test the safety and efficacy of xenon for postoperative neurocognitive deficit, we undertook a phase I study to investigate the safety of administering xenon to patients undergoing coronary artery bypass grafting while on cardiopulmonary bypass and to assess the practicability of our xenon delivery system.**

Methods: **Sixteen patients scheduled for coronary artery bypass grafting surgery with hypothermic cardiopulmonary bypass gave their informed consent to participate in an open-label dose-escalation study (0, 20, 35, 50% xenon in oxygen and air). Xenon was delivered throughout surgery using both a standard anesthetic breathing circuit and the oxygenator. Gaseous and blood xenon partial pressures were measured five times before, during, and after cardiopulmonary bypass. Middle cerebral artery Doppler was used to assess embolic load, and major organ system function was assessed before and after surgery.**

Results: **Middle cerebral artery Doppler showed no evidence of increased emboli with xenon. Patients receiving xenon had no major organ dysfunction: Troponin I and S100β levels tended to be lower in patients receiving xenon. Up to 25 l xenon was used per patient. Xenon partial pressure in the blood tracked the delivered concentration throughout.**

Conclusions: **Xenon was safely and efficiently delivered to coronary artery bypass grafting patients while on cardiopulmonary bypass. Prevention of nervous system injury by xenon should be tested in a large placebo-controlled, randomized clinical trial.**

POSTOPERATIVE neurocognitive deficit (PONCD) after cardiac surgery with cardiopulmonary bypass (CPB) represents a serious medicosocial complication.[1] The pathogenic mechanisms involved in the development of PONCD may be similar to those involved in the propagation of acute neuronal injury from other causes.[2] Glutamate may act as an excitotoxin, and antagonists of the *N*-methyl-D-aspartate (NMDA) subtype of the glutamate receptor have been protective in *in vitro* models of neuronal injury. However, clinical experience with NMDA antagonists has been less effective, and they have not been successfully exploited clinically for either PONCD or for other conditions (*e.g.*, stroke and traumatic brain injury) in which activation of the NMDA receptor is thought to be a key pathogenic factor[2]: Remacemide produced slight benefit in patients undergoing cardiac surgery[3] but has an unfavorable pharmacokinetic profile, whereas the archetypal laboratory NMDA antagonist MK801 (dizolcipine) is itself neurotoxic and cannot be used in human studies.[4]

Xenon has been shown to be an NMDA antagonist that does not exhibit the toxicity present in other drugs of this class.[5,6] Preclinical studies have demonstrated the cardioprotective[7] and neuroprotective properties of xenon.[8–13] Furthermore, the combination of xenon and mild hypothermia seems to be synergistic for neuroprotection.[14] These encouraging results, together with a favorable pharmacokinetic and pharmacodynamic profile in humans, suggest xenon as a possible intervention to protect cardiac surgical patients against neurologic injury.

Results from multicenter randomized clinical trials revealed that anesthesia with xenon provides better kinetic and safety profiles compared with other anesthetic agents in standard clinical practice[15,16] and that it is particularly appropriate for patients with compromised myocardial function.[17] However, xenon causes expansion of intravascular air bubbles that inevitably accompany cardiac surgical procedures. A theoretical model has predicted indefinite expansion of air bubbles in liquid containing dissolved xenon,[18] although experimental studies have shown a 60% increase in volume for a bubble in water[19] and a 16% increase in volume for a bubble in blood.[20] An *in vitro* oxygenator experiment found that the number of circulating bubbles greater than 20 μm in diameter increased by 10% when xenon was used as the gas source.[21] This effect may counteract any beneficial neuroprotective activity by increasing the embolic load.

This represents a dilemma: While we suspect that xenon will reduce PONCD associated with CPB, we fear that its administration might aggravate, perhaps cata-

* Honorary Senior Lecturer and Consultant Anaesthetist, Hammersmith Hospitals Trust, London, United Kingdom. † Professor, Biophysics Section, Blackett Laboratories, and Department of Anaesthetics, Pain Medicine and Intensive Care, Imperial College. ‡ Research Associate, Air Products plc, Basingstoke, United Kingdom. § Professor, National Heart and Lung Institute, Imperial College. ‖ Professor, Department of Anaesthetics, Pain Medicine and Intensive Care, and Biophysics Section, Blackett Laboratories, Imperial College.

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Address correspondence to Prof. Maze: Department of Anaesthetics, Pain Medicine and Intensive Care, Imperial College, Chelsea and Westminster Hospital, 369 Fulham Road, London SW10 9NH, United Kingdom. m.maze@imperial.ac.uk.

strophically, the very condition we hope to ameliorate. Laboratory work suggests a dose-dependent benefit from xenon, but to administer 50% xenon to a patient undergoing CPB without first using it at a lesser concentration is unjustifiable. However, it would also be unethical to undertake a study of efficacy using a low, "safe" xenon concentration if it were unlikely to demonstrate therapeutic benefit. We have compromised by undertaking an open-label, dose-escalation study measuring the embolic load and seeking evidence of damage to the organs most susceptible to gas embolism in this context (heart, kidneys, brain). Patient safety has been maximized by investing the authority to progress from one patient to the next in an independent data monitoring committee (IDMC). Successful completion of this study would provide the confidence to undertake larger scale investigations of the effect of xenon on PONCD.

Finally, xenon is a rare gas and must be used efficiently; novel equipment designed to effect this aim may increase the risk of operator error or distract the anesthesiologist from other crucial activities. We designed a device that could deliver xenon to both a standard circle system and an oxygenator, and assessed its reliability, efficiency, and ease of use during the study. We also sought to confirm that blood xenon partial pressures could be maintained during CPB.

Materials and Methods

After institutional approval (Hammersmith, Queen Charlotte's & Chelsea and Acton Hospitals Research Ethics Committee, London, United Kingdom), patients scheduled to undergo coronary artery bypass graft surgery under hypothermic CPB were recruited into an open-label xenon dose-escalation study (0, 20, 35, 50% of 1 atm); each cohort was to comprise a minimum of four patients. Consecutive eligible patients were interviewed preoperatively, and those willing to participate in the study gave written, informed consent. Exclusion criteria included a Euroscore greater than 3, atrial fibrillation, diabetes mellitus, a poor command of the English language, women of childbearing years, the need for any other concurrent cardiac or vascular procedure, neurologic injury from a previous or concurrent illness, previous or concurrent severe psychiatric illness or treatment with psychoactive drugs, known alcohol or drug dependence, treatment with hypoglycemic or cytotoxic drugs, a history of renal disease, a baseline plasma creatinine of 120 μM or greater, and exposure to an investigational drug or device in the past 12 months. The study complied with the Declaration of Helsinki.

The safety of xenon in this setting was assessed using nonspecific outcomes (duration of tracheal intubation, duration of stay in the intensive care unit and postoperatively in the hospital, readmission to the intensive care unit, hospital mortality) and outcomes specifically related to the organs deemed most at risk from increased embolism, namely, the heart (electrocardiographic evidence of myocardial infarction, unstable angina pectoris, cardiac death, postoperative troponin I), the kidneys (serum creatinine and creatinine clearance), and the brain (embolic load, major neurologic deficit, serum S100β). Information to establish the feasibility of delivering xenon using our system during cardiac surgery included the amount of xenon used, the number of operator interventions, the bias, and the root-mean-squared error between the target and the measured gas concentrations.

Patients were premedicated with 20–40 mg temazepam 1 h preoperatively. At the same time, supplementary oxygen was provided. On arrival in the anesthetic room, standard monitoring of cardiovascular and respiratory function was established. Venous access was established, and midazolam was given as required to attain a sedation score of 4 or less.[22] Another large-bore venous cannula and a 20-gauge radial arterial cannula were sited during local anesthesia. After preoxygenation, anesthesia was induced and maintained with a target-controlled propofol infusion (target 2 μg/ml), and simultaneously, a bolus of 50 μg/kg alfentanil was given, followed by a decreasing infusion of 170 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 20 min, 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for a further 20 min, decreasing to 70 $\mu g \cdot kg^{-1} \cdot min^{-1}$ thereafter (according to Stanpump,[23] this regimen establishes a target concentration of approximately 300 ng/ml). Pancuronium, 0.1 mg $\cdot kg^{-1} \cdot min^{-1}$, was administered to facilitate tracheal intubation, after which the patient's lungs were ventilated with a mixture of oxygen in air at a concentration appropriate for subsequent xenon administration (*e.g.*, when 20% xenon was to be used with 50% oxygen, 70% oxygen would be used initially to produce appropriate denitrogenation). A quad-lumen catheter was placed aseptically in the right internal jugular vein. Bifrontal electroencephalographic electrodes were applied for an Aspect A-1000 monitor (Aspect Medical Systems, Newton, MA) to record the Bispectral Index.

We developed a novel gas delivery system to minimize the use of xenon and to ensure adequate oxygenation (designed by the authors and constructed by Air Products, Basingstoke, United Kingdom; details of the device are supplied in the appendix). The device, which is intended to take on the role of a standard anesthetic machine, provides a source of oxygen in xenon to a circle breathing system at a rate so much greater than the rate of uptake by the patient that the difference between delivered concentration and inspired concentration is negligible. For efficiency, the system is closed even though an apparently high "fresh gas flow" (6 l/min) is used, for this is not fresh gas in the usual sense but rather reconditioned gas that has been scavenged from the spill valve of the circle breathing system,

scrubbed of carbon dioxide, and supplemented with oxygen and xenon. The delivery device has additional ports to supply gas to and receive exhaust gas from the oxygenator.

Xenon administration started when the anesthetized and intubated patient was transferred to the operating room, where the delivery device was already prepared. Data from the device were recorded continuously. A conventional anesthetic machine was immediately available, and conversion to an open air–oxygen breathing system could be achieved within 5 s. This conversion was to be made if there was any malfunction with the delivery device or if there was any adverse intraoperative event that was serious, unexplained, or attributable to xenon.

Samples of arterial blood were drawn at five time points during the procedure for blood xenon analysis: (1) before going on bypass; (2) 5 min after the onset of bypass; (3) before rewarming; (4) just before the end of bypass; and (5) at the end of the operation, just before discontinuing xenon administration. The partial pressure of xenon in arterial blood was determined using headspace gas chromatography. Two-milliliter samples of blood were taken from an arterial line and transferred to a 20-ml glass vial that was immediately sealed. The vials were placed in an autosampler (Perkin Elmer HS40XL; Boston, MA) connected to a gas chromatograph (Perkin Elmer Autosystem XL). The vials were equilibrated at 80°C with constant shaking for 5 min, and then 0.8 ml gas was injected into a Cromosorb 102 column (Agilent Technologies, Inc., Palo Alto, CA) (2 m × 1/8 inch packed 80–100 mesh) held at 60°C, and the xenon was detected using a thermal conductivity detector with helium as the carrier gas. The resulting peak was integrated using Turbochrom Navigator software (Perkin Elmer). Using the known xenon blood/gas partition coefficient at 37°C[24] together with the temperature dependence of xenon solubility,[25] it can be calculated that more than 99% of the xenon will be extracted into the gas phase under our conditions. A calibration curve was constructed using water equilibrated with known partial pressures of xenon to establish xenon blood concentrations in moles per liter. These concentrations were then converted to partial pressure using the known gas/saline and gas/blood partition coefficients,[24] and correcting for the observed hematocrit for each sample (assuming a linear relation).

We measured the embolic load using a 2-MHz Doppler probe (Logidop 3; Scimed Ltd., Bristol, United Kingdom) positioned over the right middle cerebral artery. The output was audible in the operating room so that xenon administration could be stopped if the load was deemed excessive. The criterion agreed on by the IDMC for terminating the study was a rate of one embolus per second for 2 min or 120 emboli in 10 min. A paper copy was printed for off-line analysis, with an embolus assumed to have occurred when a high-intensity transient signal exceeded 50% of the baseline noise. Analysis was undertaken by one investigator; expeditious communication of results to the IDMC precluded blinding.

Hypothermic CPB (using a 40-μm arterial filter) and myocardial preservation were conducted according to the surgeon's preference. Arterial blood pressure and heart rate were controlled using metaraminol, glyceryl trinitrate, atropine, or ephedrine or by adjusting doses of propofol and alfentanil, as clinically indicated, endeavoring to maintain a stable hemodynamic state (systolic arterial pressure within 20% of baseline, maximum 100 mmHg for aortic cannulation; mean arterial pressure 60 mmHg during CPB). Clinical monitoring data were stored at 2-s intervals.

Routine laboratory blood tests included daily full blood count and clotting screen (thrombin time, prothrombin time, activated partial thromboplastin time, fibrinogen), serum sodium, potassium, urea, creatinine, albumin, alkaline phosphatase, aspartate and alanine transaminases, and C-reactive protein. In addition, S100-β was measured preoperatively, at 24 and 48 h, and troponin I was measured preoperatively and at 24 h. S100-β was assayed using an automated immunoassay (Liason; DiaSorin, Saluggia, Italy). It is an immunometric assay using magnetic particle separation and a chemiluminescent endpoint. The limit of detection was 0.02 μg/l, and interassay reproducibility of quality control samples was less than 3.2%. Troponin I was also measured by an automated immunoassay (AxSYM; Abbott Diagnostics, Maidenhead, United Kingdom), which uses an enzyme label and microparticle separation. The limit of detection was 0.3 μg/l, and the reproducibility of quality controls was between 14% and 16% over the range 2.9–24 μg/l. Electrocardiograms were recorded preoperatively and on postoperative days 1, 3, and 5.

Clinical judgment was allowed to override study protocol (*e.g.*, patients in the 50% xenon cohort received no more than 40% during the rewarming phase of CPB because of the perfusionist's preference to deliver 60% oxygen at that time).

Study data were under surveillance of the IDMC, which reviewed each patient's preliminary data within 4 days of surgery. At least four patients were to be studied at each xenon concentration, with the IDMC approving the study of a further patient at that concentration or progression to the next, as appropriate. The IDMC was empowered to halt the trial or demand more patients within any cohort before allowing dose progression if they had any suspicion of an adverse effect of xenon. This decision was to be made on clinical grounds because statistical analysis was not expected to be useful with such small numbers.

Table 1. Demographic Data

Patient	Sex	Age, yr	Weight, kg	Height, cm	Euroscore	Bypass Time, min	Xclamp Time, min	CPB Temp, °C
1	M	69	96	174	2 (age 2)	99	49	34
2	M	53	100	175	0	90	44	34
3	M	60	57	165	1 (age 1)	65	37	32
4	F	69	61	160	3 (age 2, sex 1)	76	44	32
5	M	61	99	177	1 (age 1)	53	31	32
6	M	64	68	172	1 (age 1)	44	24	32
7	M	62	93	178	3 (age 1, PVD 2)	75	39	32
8	M	55	81	157	0	83	51	32
9	M	55	72	168	0	90	37	34
10	F	56	65	157	1	105	68	32
11	F	61	69	153	2 (age 1, sex 1)	87	46	32
12	M	64	78	180	1 (age 1)	82	50	32
13	M	59	70	165	0	55	33	32
14	M	52	86	170	2 (unstable angina)	77	39	32
15	M	59	79	169	2 (recent MI)	57	33	34
16	M	66	89	175	2 (age)	49	28	32

CPB temp = core temperature during cardiopulmonary bypass; MI = myocardial infarction; PVD = peripheral vascular disease; Xclamp time = duration of aortic cross-clamping.

Results

No patient study required premature termination. No extra patients were required at any xenon concentration, and with two exceptions, the IDMC approved progression to the next patient promptly. The first exception resulted from the death of patient 1 (who did not receive xenon). He had development of postoperative renal failure and died from a cardiac arrest during hemodialysis on the eighth postoperative day. The IDMC halted the study until the Research Ethics Committee completed its inquiry, which approved the continuation of the study. The second exception arose after patient 14, when we made the IDMC and the Research Ethics Committee aware of a personal communication that included some preliminary results from an animal study of deliberate carotid air embolism during xenon anesthesia:

Table 2. Clinical Outcomes

	Duration of			
Patient	Intubation, h	ICU Stay, d	Hospital Stay, d	Gastric Bubble, cm^2
1	11	7	7	0
2	9	1	6	6
3	13	1	6	0
4	11	1	6	0
5	10	1	5	0
6	9	1	6	6
7	18	1	9	38
8	17	2	9	44
9	12	1	6	3
10	12	2	13	42
11	12	2	7	39
12	6	2	6	24
13	9	1	7	14
14	7	1	6	50
15	8	4	10	11
16	8	1	6	22

ICU = intensive care unit.

The xenon group experienced greater neurologic damage (by this stage of the study, we had results of our own suggesting biochemical evidence of improved outcome in the patients receiving xenon, and there were sufficient differences in the design of the two studies for the Research Ethics Committee and IDMC to approve completion of our trial).

The groups were comparable (table 1). Two of the three female patients in the study were in the group that received 35% xenon. CPB was conducted at 32°C except for patients 1, 2, 9, and 14, who were maintained at 34°C. There were no differences between the groups in duration of CPB or duration of aortic cross-clamp.

There were no differences in duration of tracheal intubation or duration of stay in the intensive care unit and hospital (table 2). Patient 15 had development of a postoperative chest infection and remained in the intensive care unit for 4 days; patients 8, 10, 11, and 12 remained in the intensive care unit for 1 extra day because of shortage of step-down beds. Only patient 1 required renal replacement therapy. Patient 3 (no xenon) and

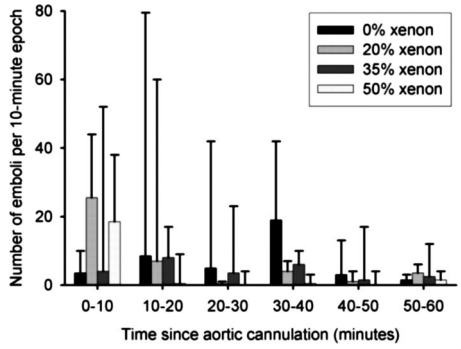

Fig. 1. Embolic load derived from high-intensity transient signals (HITS) on the middle cerebral artery Doppler recording. For each patient cohort, the median number of HITS within each 10-min epoch is plotted: *Error bars* indicate the maximum for that cohort.

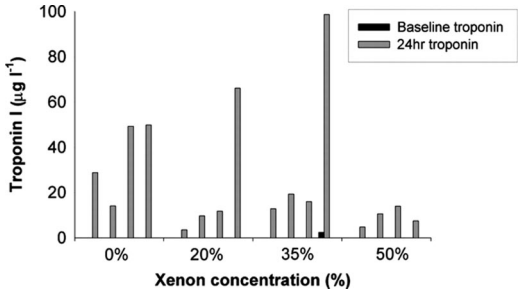

Fig. 2. Baseline and 24-h troponin I (laboratory upper limit of normal: < 0.5 μg/l so only abnormal results are visible on the plot).

patient 10 (35% xenon) had development of electrocardiographic changes compatible with myocardial infarction, although in neither case was hospital discharge delayed. There were no clinical neurologic injuries and no differences in routine laboratory test results between the groups. There were no significant differences in the total number of emboli or their temporal distribution between patient groups (fig. 1). Patient 12 (xenon 20%) had a high baseline troponin I, suggesting an unsuspected acute preoperative coronary event, and also had the highest postoperative value; despite this, there was no overall increase in troponin associated with xenon administration, nor was there any increase in postoperative S100β (figs. 2 and 3 and table 3).

An incidental finding from routine chest radiographs, discovered after the study had ended, was that several of the patients who received xenon had large gastric bubbles on the first postoperative day (table 2: $P < 0.05$ for the Cuzick trend in cross-sectional area across groups), but this did not result in an adverse outcome.

The delivery system proved reliable, although electronic data were not collected for patient 10 through a simple operator error (the recorder was not turned on). No more than 25 l xenon was used for any xenon-receiving patient, including gas used during machine checks and preparing the device some hours in advance. The maximum xenon used during the time a patient was exposed was less than 20 l. The device required periodic interventions by the operator (approximately 5/h), usually to rid the breathing system of nitrogen but also to vent the system of excess volume after an increase in the target oxygen concentration or, in the earlier patients, to add air after excessive denitrogenation led to the xenon concentration exceeding its target.

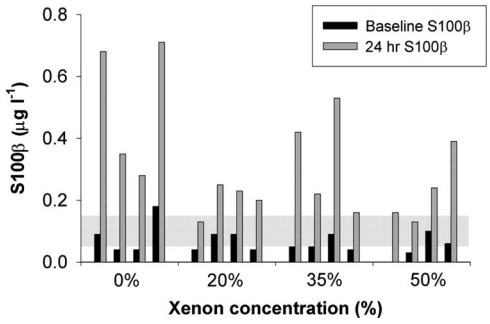

Fig. 3. Baseline and 24-h S100β. The *shaded area* shows the laboratory reference range of 0.05–0.15 μg/l. (The baseline result for the first patient in the 50% xenon group is not available.)

Table 3. Biochemical Outcomes

	Serum Creatinine, μM			S100-β, μM		Troponin I, μM	
Patient	Baseline	Max Postop	Creatinine Clearance, ml/min	Baseline	24 h	Baseline	24 h
1	113	419	20	0.09	0.68	< 0.3	28.8
2	98	95	174	0.04	0.35	< 0.3	14.1
3	85	86	85	0.04	0.28	< 0.3	49.3
4	80	85	109	0.18	0.71	< 0.3	49.9
5	74	89	—	0.04	0.13	< 0.3	3.6
6	105	124	73	0.09	0.25	< 0.3	9.7
7	121	139	109	0.09	0.23	< 0.3	11.8
8	88	92	84	0.04	0.2	< 0.3	66.2
9	100	115	98	0.05	0.42	< 0.3	12.9
10	76	83	122	0.05	0.22	< 0.3	19.3
11	77	101	—	0.09	0.53	< 0.3	16
12	90	92	—	0.04	0.16	2.5	98.7
13	81	94	94	—	0.16	< 0.3	4.8
14	113	115	80	0.03	0.13	< 0.3	10.6
15	91	95	131	0.1	0.24	< 0.3	14
16	108	133	91	0.06	0.39	< 0.3	7.5

Max postop = maximum value recorded in the postoperative period.

The partial pressure gradients between xenon in delivered gas and in blood are shown in figure 4. The expected blood xenon partial pressure was not achieved before CPB in any patient, but there was no correlation between duration of xenon administration before the first sample (mean, 49 min; range, 33–75 min) and the

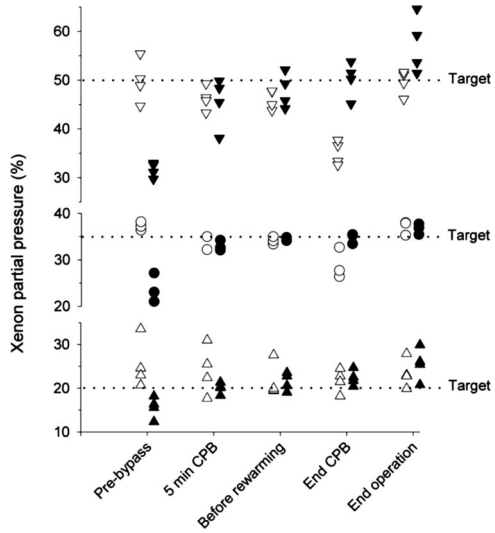

Fig. 4. Partial pressure of xenon in delivered gas and blood. Samples were drawn at five points during the operation as shown on the horizontal axis. Gas partial pressures are shown in *open symbols* and are mean values of measurements recorded during 1 min centered on the time of drawing the blood sample. Blood partial pressures are shown in *closed symbols*. △,▲ = 20% cohort; ○,● = 35% cohort; ▽,▼ = 50% cohort; CPB = cardiopulmonary bypass.

gas–blood partial pressure gradient (absolute or relative). During CPB, the target partial pressure was maintained even when the delivered concentration was reduced to allow increased oxygen delivery.

Discussion

Xenon was administered during cardiac surgery without producing adverse clinical consequences in this phase I study. In particular, we found no evidence of increased embolic load or organ injury. The limited number of patients (n = 12) exposed to xenon precludes our making definitive interpretations regarding its safety in this clinical setting but provides confidence to proceed with a larger study.

The gas delivery equipment proved reliable and easy to use. The use of a 6-l/min flow to the circle system meant that the anesthesiologist operated in a familiar fashion, untroubled by the demands of completely closed system anesthesia. Although several interventions were made during every case, none was essential to patient safety. A simple, automatic venting system may be introduced on later machines to minimize the attention required; combined with a waste collection system, this should reduce the xenon usage to less than 20 l fresh xenon per patient. We have no explanation for the low partial pressure of xenon in blood before CPB. We did not measure the inspired xenon concentration, but calculation led us to expect that if we delivered 5 l/min to the breathing system, there would be little difference between delivered and inspired concentrations. Transfer *via* the oxygenator was efficient, and the gradient between delivered and blood partial pressures was negligible after 5 min of CPB. Given this efficiency, it was surprising to find that the blood xenon partial pressure was maintained during CPB when the delivered concentration was reduced.

The Doppler device placed over the middle cerebral artery counts embolic load without providing information on size or composition. With current technology, a dual-channel Doppler may be more appropriate to estimate size and composition of emboli; however, at the time that this study was initiated, its performance had not yet been independently verified. However, if xenon induced significant bubble expansion, we would expect the number of emboli we recorded to increase because bubbles previously below the threshold of sensitivity would have become detectable; no such increase occurred.

Troponin is a reliable index of myocardial injury, and we would expect it to increase if coronary air embolism occurs. There was no increase in troponin associated with xenon administration, and in fact, *post hoc* analysis revealed a tendency for the concentration at 24 h to be lower in the patients receiving xenon (this effect is much stronger if the patient with the increased baseline troponin is excluded). Preclinical studies have found that injury after myocardial stunning is reduced by xenon,[7] so the troponin results may reflect myocardial protection. However, given that the study was not randomized, we can only report that we have found no evidence of increased myocardial injury with xenon administration.

S100β is a relatively nonspecific marker of cerebral injury; we found no evidence of increase of this analyte in the patients receiving xenon. Just as with troponin, *post hoc* analysis suggests a reduction in postoperative S100β in patients receiving xenon, but again, there are other possible explanations for this result (*e.g.*, erythrocyte salvage is being used increasingly at our institution). As with the troponin results, we draw attention to the apparent reduction in postoperative S100β only to indicate that our failure to find evidence of an increase does not seem to be due to the small numbers in our study.

Varying degrees of neurologic damage may occur in cardiac surgical patients; stroke, the most severe form of such damage, occurs in approximately 2–5% of patients. The incidence of the more subtle neurocognitive deficit is as high as 80% in the early postoperative period after cardiac surgery, although it decreases to approximately 20–40% at 3 months and approximately 15–25% at 1 yr[1]; the incidence is also high in patients who have cardiac surgery without CPB.[26] The impact of neurocognitive dysfunction is substantial, both on patients' quality of life and on healthcare resource utilization.[27] Xenon is an attractive anesthetic for cardiac surgery because it provides clinical hemodynamic stability[15,16] and there is preclinical evidence of cardioprotection and neuroprotection, especially during hypothermia.[7–14] Cost has so far precluded its routine use, but the consumption of xenon was modest with our delivery system. Were neuroprotection to be demonstrated clinically, cost would not preclude its implementation. This study predicates the need for an appropriately powered, randomized, placebo-controlled, clinical trial of xenon during cardiac surgery to test its neuroprotective efficacy.

The independent data monitoring committee involved with this study comprised Anita Holdcroft, M.B., Ch.B., M.D., F.R.C.A. (Reader in Anaesthesia and Honorary Consultant Anaesthetist, Chelsea and Westminster Hospital, Faculty of Medicine, Imperial College of London, London, United Kingdom), and Janusz Bernard Liban, M.B., Ch.B., F.R.C.A. (Consultant Anaesthetist, St. George's Hospital, Tooting, London, United Kingdom).

References

1. Newman MF, Kirchner JL, Phillips-Bute B, Gaver V, Grocott H, Jones RH, Mark DB, Reves JG, Blumenthal JA: Longitudinal assessment of neurocognitive-function after coronary-artery bypass surgery. N Engl J Med 2001; 344:395–402

2. Lynch DR, Guttmann RP: Excitotoxicity: Perspectives based on N-methyl-D-aspartate receptor subtypes. J Pharmacol Exp Ther 2002; 300:717–23

3. Arrowsmith JE, Harrison MJ, Newman SP, Stygall J, Timberlake N, Pugsley WB: Neuroprotection of the brain during cardiopulmonary bypass: A randomized trial of remacemide during coronary artery bypass in 171 patients. Stroke 1998; 29:2357–62

4. Fix AS, Wozniak DF, Truex LL, McEwen M, Miller JP, Olney JW: Quantitative analysis of factors influencing neuronal necrosis induced by MK-801 in the rat posterior cingulate/retrosplenial cortex. Brain Res 1995; 696:194–204
5. Franks NP, Dickinson R, De Sousa SL, Hall AC, Lieb WR: How does xenon produce anaesthesia? (letter). Nature 1998; 396:324
6. Ma D, Wilhelm S, Maze M, Franks NP: Neuroprotective and neurotoxic properties of the "inert" gas, xenon. Br J Anaesth 2002; 89:739–46
7. Preckel B, Müllenheim J, Moloschavij A, Thämer V, Schlack W: Xenon administration during early reperfusion reduces infarct size after regional ischemia in the rabbit heart *in vivo*. Anesth Analg 2000; 91:1327–32
8. Wilhelm S, Ma D, Maze M, Franks NP: Effects of xenon on *in vitro* and *in vivo* models of neuronal injury. ANESTHESIOLOGY 2002; 96:1485–91
9. Homi HM, Yokoo N, Ma D, Warner DS, Franks NP, Maze M, Grocott HP: The neuroprotective effect of xenon administration during transient middle cerebral artery occlusion in mice. ANESTHESIOLOGY 2003; 99:876–81
10. Ma D, Yang H, Lynch J, Franks NP, Maze M, Grocott HP: Xenon attenuates cardiopulmonary bypass–induced neurologic and neurocognitive dysfunction in the rat. ANESTHESIOLOGY 2003; 98:690–8
11. Petzelt C, Blom P, Schmehl W: Prevention of neurotoxicity in hypoxic cortical neurons by the noble gas xenon. Life Sci 2003; 72:1909–18
12. Schmidt M, Marx T, Gloggl E, Reinelt H, Schirmer U: Xenon attenuates cerebral damage after ischemia in pigs. ANESTHESIOLOGY 2005; 102:929–36
13. Ma D, Hossain M, Pettet GKJ, Luo Y, Lim T, Akimov S, Sanders RD, Franks NP, Maze M: Xenon preconditioning reduces brain damage from neonatal asphyxia in rats. J Cereb Blood Flow Metab 2006; 26:199–208
14. Ma D, Hossain M, Chow A, Arshad A, Battson RM, Sanders RD, Hehmet H, Edwards AD, Franks NP, Maze M: Xenon and hypothermia combine to provide neuroprotection from neonatal asphyxia. Ann Neurol 2005; 58:182–93
15. Rossaint R, Reyle-Hahn M, Schulte Am Esch J, Scholz J, Scherpereel P, Vallet B, Giunta F, Del Turco M, Erdmann W, Tenbrinck R, Hammerle AF, Nagele P, Xenon Study Group: Multicenter randomized comparison of the efficacy and safety of xenon and isoflurane in patients undergoing elective surgery. ANESTHESIOLOGY 2003; 98:6–13
16. Coburn M, Kunitz O, Baumert J-H, Hecker K, Haaf S, Zühlsdorff A, Beeker T, Rossaint R: Randomized controlled trial of the haemodynamic and recovery effects of xenon or propofol anaesthesia. Br J Anaesth 2005; 94:198–202
17. Baumert JH, Falter F, Eletr D, Hecker KE, Reyle-Hahn M, Rossaint R: Xenon anaesthesia may preserve cardiovascular function in patients with heart failure. Acta Anaesthesiol Scand 2005; 49:743–9
18. Sta Maria N, Eckmann DM: Model predictions of gas embolism growth and reabsorption during xenon anesthesia. ANESTHESIOLOGY 2003; 99:638–45
19. Lockwood G: Expansion of air bubbles in aqueous solutions of nitrous oxide or xenon. Br J Anaesth 2002; 89:282–6
20. Grocott HP, Sato Y, Homi HM, Smith BE: The influence of xenon, nitrous oxide and nitrogen on gas bubble expansion during cardiopulmonary bypass. Eur J Anaesthesiol 2005; 22:353–8
21. Casey ND, Chandler J, Gifford D, Falter F: Microbubble production in an *in vitro* cardiopulmonary bypass circuit ventilated with xenon. Perfusion 2005; 20:145–50
22. Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, Schwam EM, Siegel JL: Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: Study with intravenous midazolam. J Clin Psychopharmacol 1990; 10:244–51
23. Black ML, Hill JL, Zacny JP: Behavioral and physiological effects of remifentanil and alfentanil in healthy volunteers. ANESTHESIOLOGY 1999; 90:718–26
24. Goto T, Suwa K, Uezono S, Ichinose F, Uchiyama M, Morita S: The blood-gas partition coefficient of xenon may be lower than generally accepted. Br J Anaesth 1998; 80:255–6
25. Smith RA, Porter EG, Miller KW: The solubility of anesthetic gases in lipid bilayers. Biochim Biophys Acta 1981; 645:327–38
26. van Dijk D, Moons KG, Keizer AM, Jansen EW, Hijman R, Diephuis JC, Borst C, de Jaegere PP, Grobbee DE, Kalkman CJ, Octopus Study Group: Association between early and three month cognitive outcome after off-pump and on-pump coronary bypass surgery. Heart 2004; 90:431–4
27. Newman MF, Grocott HP, Mathew JP, White WD, Landolfo K, Reves JG, Laskowitz DT, Mark DB, Blumenthal JA, Neurologic Outcome Research Group and the Cardiothoracic Anesthesia Research Endeavors (CARE) Investigators of the Duke Heart Center: Report of the substudy assessing the impact of neurocognitive function on quality of life 5 years after cardiac surgery. Stroke 2001; 32:2874–81

Appendix: Device for Delivery of Xenon to Both a Breathing System and an Oxygenator for CPB

Overview

The device, which is intended to take on the role of a conventional anesthetic machine, provides a source of oxygen in xenon to a circle breathing system at a rate so much greater than the rate of uptake by the patient that the difference between delivered concentration and inspired concentration is negligible. For efficiency, the system is closed, although an apparently high "fresh gas flow" (6 l/min) is used. Technically, this is not fresh gas in the usual sense but rather reconditioned gas that has been scavenged from the conventional breathing system, scrubbed of carbon dioxide, and supplemented with oxygen and xenon. The machine was designed and constructed by Air Products (Basingstoke, United Kingdom) in consultation with the authors.

Internal Circle

Gas is circulated by a pump containing two chambers, each with one flexible wall that is compressed intermittently, generating flow past simple flutter valves. There is therefore no mechanism by which dangerously high pressures could occur, even if the outflow was obstructed. Downstream of the pump, pressure is generated and regulated by a weighted valve, and the flow returns to the pump inlet. Gas can be drawn from the pressurised section of the internal circle through rotameters for delivery either to the conventional breathing system or to the oxygenator. Gas is also bled across the pressurized valve through sidestream oxygen and carbon dioxide analyzers.

As the gas circulates in the internal circle, it passes through soda lime and silica gel chambers, removing carbon dioxide and excess water vapor. Immediately before return to the pump, there is a rising bellows gas reservoir and a return port for scavenged gas.

The patient and the complete breathing system must be denitrogenated before xenon delivery starts because residual nitrogen will limit the concentration of xenon that can be achieved without hypoxia. The patient is denitrogenated to an appropriate level for 15–20 min, and the complete breathing system is denitrogenated (by manually operating an oxygen flush and a vent that empties the reservoir bellows) before the two are connected. The conventional breathing system must be leak free to provide conditions for a closed system.

Avoidance of Hypoxia

Delivery of fresh oxygen to the gases within the delivery device is under automatic control, and there is also a simple manual flush. If the concentration of oxygen within the system is less than the target concentration (never less than 30%), oxygen is delivered at a rate proportional to the difference between the two. The concentration of oxygen within the breathing system is measured by a fuel cell (Teledyne R-17VAN; Teledyne Analytical Instruments, City of Industry, CA), calibrated before each use. The fuel cell is located in the main stream of the circulating gas, and it is used for a "low oxygen" alarm that operates below 30% oxygen. There is also a paramagnetic analyzer (Paracube Pm111E701; Servomex Group Ltd., Crowborough, United Kingdom) that acts to confirm the primary analyzer but uses a different physical principle for measurement.

The device is fitted with an uninterruptible power supply, but in the event of an internal power failure, the oxygen flow controller becomes fully on while the xenon flow controller shuts off. Should the xenon flow controller malfunction, hypoxia is prevented because the cylinders are filled with a mixture of 80% xenon in oxygen.

Delivery of Xenon

The volume of the reservoir within the internal circle is shown by the height of the bellows, which is measured ultrasonically. Xenon is added according to a simple, proportional algorithm that is hardwired electronically to maintain a constant system volume. As the patient consumes oxygen and the reservoir volume reduces, xenon is added and the concentration within the system increases, limited only by both the demand that the target oxygen concentration is maintained and by residual nitrogen. Therefore, the system achieves the greatest concentration of xenon compatible with the desired oxygen concentration and the residual nitrogen concentration while maintaining closure of the complete breathing system. An ultrasonic device situ-

ated in the main stream of circulating gas measures xenon concentration, but it is not involved in control processes.

Monitoring

Flowmeters on the front panel show oxygen and xenon inflows, flow to and from the oxygenator, flow to the conventional circle breathing system (flow from the system is not helpfully monitored by a rotameter because of its discontinuous nature), and flow to the sidestream gas analyzers. These flowmeters are influenced by the gas composition, but at least they reliably provide estimates of flow at all times. The flow to the oxygenator is also measured by a Pelton wheel, which is less influenced by gas density and displayed electronically.

The pressure in the pressurised section of the internal circle is displayed both electronically and by a Magnahelic low-pressure diaphragm gauge (Dwyer Instruments Inc., Michigan City, IN). The pressure at the oxygenator outlet is also measured electronically, and an alarm triggers if it becomes excessive.

An ultrasonic analyzer measures xenon concentration within the main circulating gas stream. It has been tested against a mass spectrometer and has a deviation of less than 2% absolute (data not shown). Gas monitoring also includes two oxygen analyzers (see above) and two infrared carbon dioxide analyzers (IR21CA; e2v Technologies Ltd., Chelmsford, United Kingdom), one situated in the return gas from the oxygenator and one in a sidestream of the main circulating gas.

Finally, an additional oxygen monitor is required in the conventional breathing system because the patient inspires a mixture of "fresh" gas and scrubbed, expired gas. This is not needed on the oxygenator because it receives gas exclusively from the delivery device.

Alarms

Some of the alarms on the device have been already mentioned, but the complete list comprises oxygen concentration, oxygen measurement error, low internal circle system pressure, reservoir bellows at maximum (resulting in spill of system gas) or too low (potentially entraining air), and high pressure in outlet to oxygenator. The rotameters for gas running to and from the oxygenator have optical sensors at the 1-l/min mark. When either bobbin descends past its sensor, a "low flow" alarm is raised.

Oxygenator Supply

Oxygenator design is strongly influenced by the concern of damage through overpressure, which could happen if the gas outlet were occluded, and few therefore allow the effective scavenging of exhaust gas. We have used the Medos Hilite 7000 oxygenator (Medos Medizintechnik AG, Stolberg, Germany), which can easily be modified to allow exhaust gas collection. This modification exposes the oxygenator to the risk of gas overpressure. This risk was obviated by a water trap blowing off at 10 cm H_2O placed in the supply line.

A "buddy box" was built to allow the perfusionist control over gas delivery to the oxygenator, duplicating some of the controls and monitoring available on the delivery device itself. This allows the target oxygen concentration and the flow to the oxygenator to be set remotely. Although the rotameter through which gas passed to the oxygenator is fitted with a needle valve, this is normally fully open, and flow is controlled electronically. To minimize the effect of xenon in the gas mixture, the flow to the oxygenator is under feedback control from the Pelton wheel; the needle valve is available in case of failure of the electronic system.