CLINICAL CONCEPTS AND COMMENTARY

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Xenon Anesthesia

Carl Lynch III, M.D., Ph.D., Jan Baum, Prof.Dr.Med.,† Rob Tenbrinck, M.D., Ph.D.‡*

ALONG with helium, neon, argon, krypton, and radon, xenon is one of the noble gases, *i.e.*, it is an element whose outer shell is filled with electrons. Although the two lowest-molecular-weight noble gases, helium and neon, have very small electron shells and no anesthetic actions, the anesthetic properties of xenon have been recognized for almost 50 yr.[1] With its filled outer electron shell, xenon exists as a monatomic gas under normothermic and normobaric conditions. Although it is virtually inert and does not form covalent bonds with other elements (except under extreme conditions), the very large electron shell of xenon can be polarized and distorted by nearby molecules (creating an induced dipole). This distortion of the electron orbitals permits xenon to interact with and bind to proteins such as myoglobin[2] as well as to bilayer lipids, particularly in the region of the more polar headgroups.[3] Its oil/gas partition coefficient of 1.9 is higher than the lighter noble gases. The ability of xenon to interact with cell proteins and cell membrane constituents is presumably responsible for its anesthetic potency. Xenon inhibits the plasma membrane Ca^{2+} pump,[4] an action similar to that of volatile anesthetics, which may be responsible for an increase in neuronal Ca^{2+} concentrations and altered excitability. Xenon seems to inhibit the nociceptive responsiveness of spinal dorsal horn neurons,[5] an effect that may be mediated by inhibition of *N*-methyl-D-aspartate receptors.[6]

With a blood/gas partition coefficient of 0.115, xenon is the least soluble gas that may be used for anesthesia.[7] During the past decade, it has received increasing study as an anesthetic agent with many attractive properties. Based on abstracts and reports in the literature, xenon has been shown to not alter voltage-gated ion channels in the myocardium,[8] nor does it sensitize the myocardium to the dysrhythmogenic effects of epinephrine.[9] Studies in patients[10] and in cardiomyopathic dogs[11] have demonstrated that xenon does not depress the myocardial contractility. Effects on the vasculature remain to be better defined, but xenon has no apparent effects on mesenteric vascular resistance. This apparent lack of effect in cardiovascular tissues may be responsible for its minimal effects on the cardiovascular system and may make xenon particularly useful in situations in which cardiovascular stability needs to be maintained. In addition to cardiovascular stability, a number of features makes xenon a nearly ideal anesthetic gas: rapid induction and emergence, a sufficient analgesic and hypnotic effect in a mixture with 30% oxygen, the absence of metabolism, undisturbed ventilation and pulmonary function, and lack of triggering of malignant hyperthermia. With a human minimum alveolar concentration value of 0.71[12] (> twofold higher in some other species; table 1), the gas is optimally suited to be used as an inha-

* Robert M. Epstein Professor and Chair, Department of Anesthesiology, University of Virginia Health System, Charlottesville, Virginia.

† Professor, Departments of Anesthesiology and Intensive Care, Hospital St. Elisabeth-Stift, Damme, Germany.

‡ Department of Anesthesiology, Hospital Dijkzigt, Erasmus University, Rotterdam, The Netherlands.

Received from the Department of Anesthesiology, University of Virginia Health System, Charlottesville, Virginia; the Departments of Anesthesiology and Intensive Care, Hospital St. Elisabeth-Stift, Damme, Germany; and the Department of Anesthesiology, Hospital Dijkzigt, Erasmus University, Rotterdam, The Netherlands. Submitted for publication December 23, 1998. Accepted for publication September 21, 1999. Support was provided solely from institutional and/or departmental sources.

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Address reprint requests to Dr. Lynch: Department of Anesthesiology, University of Virginia Health Sciences Center, Box 10010, Charlottesville, Virginia 22906-0010. Address electronic mail to: carllynch@virginia.edu

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Table 1. Physical and Biologic Characteristics of Xenon

Melting point (°C)	−111.9	
Boiling point (°C)	−108.1	
Ostwald solubility coefficients		
(ml gas/ml liquid)	At 37°C	At 25°C
Water/gas	0.075	0.095
Oil/gas	1.8	1.9
PC bilayer/gas		1.36
PC and chol.bilayer/gas		1.23
octanol/water		19.1
Blood	0.115	
Muscle, lung, kidney	0.10	
Brain, gray matter	0.13	
Brain, white matter	0.23	
MAC (fraction of atmosphere)		
Human	0.71	
Dog	1.19	
Rat	1.61	
Mouse	0.95	

Compiled from references 7, 20–22.

lation anesthetic in a mixture with 30% oxygen. However, at concentrations > 60%, xenon increases the cerebral blood flow,[10] and there can be retention of a considerable amounts of the gas in the bowels and fatty tissues. Up to this point, no data are available concerning the suitability of xenon in patients suffering from increased intracranial pressure or bowel obstruction. Nevertheless, the use of xenon as an anesthetic agent is promising and has been submitted for regulatory medical approval in Europe.

Except for radon, xenon is the rarest noble gas, being present in atmospheric air in a concentration of no more than 0.086 ppm. Thus, the air of a normal living room with a volume of 50 m^3 contains only 4 ml xenon. The high molecular weight of xenon (131.2 d) gives it a density more than four times greater than air. Xenon is recovered in the process of air liquification, and after several separation processes, a purity of 99.995% can be obtained. The current world production of xenon is approximately six million liters per year. One million liters of xenon per year is already expended in medical uses, with half of this amount being used for anesthetic purposes.[13] Xenon has been used for decades to study blood flow and gas distribution in the lung, although recent technical developments have expanded its use in magnetic resonance imaging.[14] The yearly production is predicted to increase during the next 3 yr to 9.5 million liters. Currently, there is an increasing demand for this gas because of a recently launched project by the United States aerospace industry that uses xenon ion engines to maneuver satellites.

Corresponding to its rarity, xenon is expensive. During the last 2 yr, the price has increased from approximately $5 (U.S.) to approximately $10 per liter, and further changes are unpredictable. Because xenon is rare and expensive, the use of this gas as an anesthetic agent can be justified only if its waste is reduced to the absolute minimum. It must be applied *via* rebreathing systems using the lowest possible gas flows. If 70% xenon is administered using a fresh gas flow as low as 0.5 l/min, during a 2-h anesthetic procedure, the efficiency would not even reach 20%, *i.e.*, less than 20% of the xenon delivered into the breathing system would actually be taken up by the patient, leaving > 80% (approximately 34 l) to be spilled out into the atmosphere as waste. Closed-system anesthesia is the only economically acceptable technique for application of xenon for anesthetic purposes. An electronically controlled anesthesia delivery system that continuously monitors gas concentrations inside the breathing circuit may be used for this purpose (xenon concentration can be determined by heat conductivity or by a characteristic radiofrequency response). A closed loop-feedback control mechanism delivers xenon and oxygen into the system in the amount needed to maintain constant gas concentrations and circulating gas volume. The usual manual control of a closed circuit may also be used. Because of its high density, the presence of xenon may degrade the accuracy of certain respiratory flowmeters.[15]

For practical clinical use, nitrogen must first be washed out on induction of anesthesia by applying high-flow pure oxygen over a period of at least 5 min, typically accompanied by administration of a combination such as fentanyl (3 μg/kg), propofol (2 mg/kg), and a muscle relaxant. After endotracheal intubation, the patient is connected to the ventilator of an appropriate anesthetic delivery system. The hypnotic concentration of 40–45% xenon is established after 1.5 min, reaching the desired concentration of 60–70% in approximately 8 min. A small supplementary dose of fentanyl may be given just before skin incision.

If xenon is applied *via* a closed rebreathing system after complete denitrogenation, 60–70% inspired xenon results in approximately 6 l being taken up in the first hour in an average adult, with 9–15 l being consumed in the first 2 h of xenon administration (fig. 1A).[16] Some of the gas taken up may be lost to the atmosphere from the skin and surgically exposed tissues. Washout of the drug follows a similar time course (fig. 1B). Because xenon is substantially less soluble than nitrous oxide, its equilibration and washout causes less diffusion hypoxia.[17] In addition, its low solubility permits a faster emergence

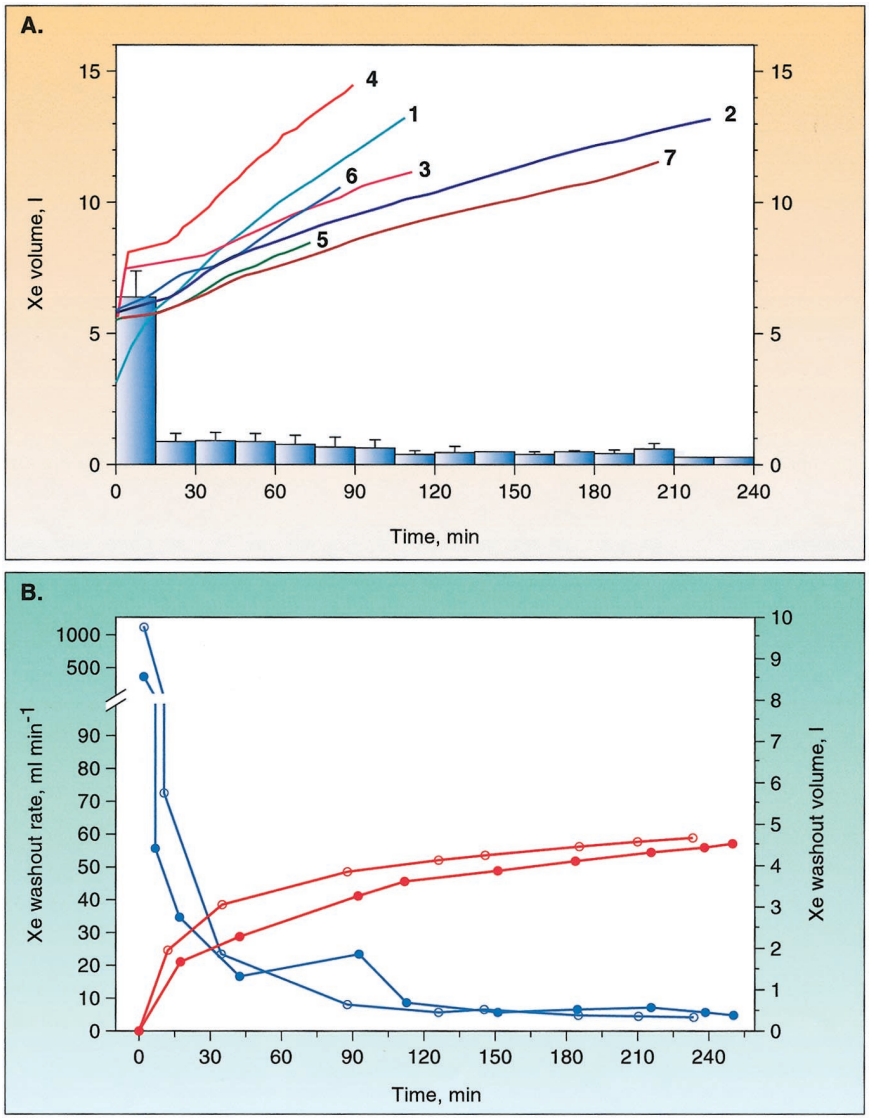

Fig. 1. Uptake and elimination of xenon from patients undergoing surgical procedures. (*A*) Uptake curves and mean uptake amounts (in liters) of xenon in seven patients (average weight = 72 ± 12 kg) after prior denitrogenation by breathing 100% oxygen for 15–20 min. (*B*) Washout of xenon from patients no. 6 and 7 in (*A*). (Reprinted from Luttropp *et al.*[16] with permission.)

than with nitrous oxide[18] that is unaltered by the duration of the anesthetic.[19]

If the total yearly production of approximately six million liters of xenon were available exclusively for anesthetic purposes, not more than 400,000 anesthetic procedures could be performed with this amount of gas. Recycling of the xenon contained in the gas escaping *via* the exhaust port rather than wasting it into the atmosphere is the only way to guarantee the availability of a sufficient amount of xenon for routine use as an anesthetic gas in clinical practice. With currently available prototypes of recycling devices, approximately 70–90% of the xenon delivered into the system can be recovered, with a purity of approximately 90%. Oxygen and nitrogen make up the bulk of the impurities.

Because of its considerable expense and the fact that it cannot be synthesized, but rather must be extracted from the atmosphere, it is unlikely that xenon will gain widespread use. However, should delivery systems (closed circuit) become available with appropriate techniques for recycling the gas, xenon anesthesia may become more readily available. It may be a highly useful alternative in selected patients, *e.g.*, those with limited cardiovascular reserve. Over the next few years, it will be interesting to see better definition of its pharmacologic characteristics at the cellular level, as well as its effects and cost–benefit ratio in clinical trials.

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The following correspondence§ refers to a previously published Clinical Concepts and Commentary article by Eisenach (Eisenach JC: Combined spinal–epidural analgesia in obstetrics. ANESTHESIOLOGY 1999; 91:299–302).

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Another Possible Indication for the Combined Spinal–Epidural Technique in Obstetrics

To the Editor:—I read with great interest Dr. Eisenach's excellent article concerning combined spinal–epidural analgesia in obstetrics. Although the limitations of the technique are well stated,[1] I have been using the technique routinely in obstetrics for several years and recently discovered what I regard as a somewhat unusual but useful indication.

I was recently called to consult on an obstetric patient who was being induced at 37 weeks' gestation for severe preeclampsia. Her liver enzymes were mildly elevated and her platelet count was decreasing. At the time of the consult, platelet count was 130,000/μl but had

§ Richard B. Weiskopf, M.D., was Acting Editor-in-Chief for this correspondence.