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A Minimal-flow System for Xenon Anesthesia

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We describe a minimal-flow system for xenon anesthesia during controlled ventilation. A computer maintained oxygen concentration in the anesthesia circle within ± 2% of the value set by the anesthesiologist. The ventilator and the circle were connected *via* a large dead space, through which oxygen from the ventilator entered the circle but which prevented xenon from escaping. This arrangement simplified the computer program. The system was tested on a lung model and in six pigs (37–39 kg). The xenon expenditure and the amount of xenon washed out from the pigs after the anesthetic were measured. Additional experiments with nitrous oxide were made in three pigs. The xenon expenditure during 2 h of xenon anesthesia was 7.6 ± 0.8 l (mean ± 1 standard deviation). The corresponding expenditure of nitrous oxide was 16.5 ± 2.7 l. About 75% of the xenon expenditure was in the 1st h of anesthesia; thereafter, 20–40 ml · min^{-1} was needed to maintain oxygen concentration at 30%. Nitrogen concentration in the circle increased to 12–16% during the xenon anesthetic, although it was preceded by a 20 min denitrogenation period. During the washout phase after the xenon anesthesia, mean expired xenon concentration decreased to below 2% within 4 min. Subsequently, washout was slower and the expired concentration remained above 0.1% for more than 90 min. The estimated total amount of xenon washed out from the lungs and body tissues during 4 h of oxygen breathing was about 4 l. We conclude that xenon anesthesia *via* a fully automated minimal-flow system is feasible. About half of the xenon delivered by the system was taken up in the body. The decrease in expired concentration to less than 0.05 MAC was very rapid, after discontinuation of the xenon inhalation. (Key words: Anesthetics, gases: xenon. Anesthetic techniques: low-flow. Automatic data processing.)

THE RARE GAS XENON has anesthetic properties,[1] and its MAC is approximately 71%.[2] Xenon, like helium, is one of the noble gases, and as such belongs to group 0 in the periodic table. In these elements, the atom has a fully occupied outer electron shell; xenon is therefore unreactive, and is unlikely to take part in chemical reactions in the body. Other advantages are its potency, which is greater than that of nitrous oxide,[3] and the rapid recovery from xenon anesthesia,[4] the latter of which is consistent with the low blood–gas solubility coefficient of 0.14[5] (37° C). Were it not for high cost, xenon would be a valuable alternative to nitrous oxide. One way of reducing costs is to administer xenon *via* a rebreathing circuit with a minimal fresh gas flow. The present study describes a minimal-flow system for xenon anesthesia, which uses feedback control by computer to maintain oxygen concentration in the anesthesia circle at the desired level. The volume of xenon used and its washout after the exposure were studied in pigs.

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Materials and Methods

Design and Working Principles

The system (Fig 1) consisted of three parts: an anesthesia circle with carbon dioxide absorber and one-way valves, a ventilator, and a large dead space in the form of a tube connecting the two (the "exchanger"). The ventilator (Servo 900 C, Siemens) delivered 100% oxygen. We used the exchanger instead of a traditional "bag-in-bottle" arrangement with bellows. The primary function of the exchanger was to transmit the pressure and volume variations generated by the ventilator. A second function was to partially isolate the circle from the ventilator, thereby reducing loss of xenon from the circle; it was part of the concept, however, that oxygen from the ventilator slowly entered the circle (see below). The exchanger was made of polyvinyl chloride with internal diameter and volume of approximately 3.3 cm and 3 l, respectively. Because of its width, there was virtually no pressure gradient along the exchanger during inspiration and expiration.

Xenon and oxygen of high purity (99.995%) were supplied to the circle *via* magnetic valves (Festo MFM-2-M5), the opening times of which were governed by a computer (Panasonic FT80) *via* a multifunction input–output board (Analog Devices RTI-815). The valves were open only during expiration, in order that the inspired tidal volume should not be affected by the intermittent boluses of infused gas. The maximum bolus volume was 200 ml. If a greater amount was needed, it was delivered over several expirations. The computer was connected *via* an analog–digital interface to a Siemens Anesthesia Gas Monitor 120, which measured oxygen concentration at the Y-piece. The 90% response time of the analyzer to a step change in oxygen concentration was 30 s. Because of this relatively slow response, measured oxygen concentration represented a time average of expired and inspired concentrations. If oxygen concentration was outside the desired limits, the computer initiated the infusion of a bolus of xenon or oxygen into the circle *via* the appropriate magnetic valve. However, the oxygen supply to the circle was mainly from the ventilator: since the carbon dioxide pro-

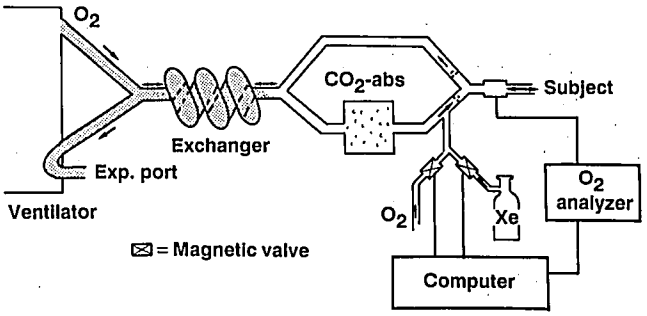

FIG. 1. The minimal flow system. The ventilator and circle are separated by a large (3-l) deadspace ("the exchanger"). During steady-state conditions, oxygen from the ventilator (shaded) reaches into most of the exchanger, and very little xenon escapes from the anesthesia circuit. Oxygen concentration in the circuit is governed by the computer, which delivers xenon or oxygen as needed *via* the magnetic valves. CO_2-abs = carbon dioxide absorber; Exp. port = expiratory port of ventilator.

duced was absorbed by the soda lime, the gas volume in the circle decreased as oxygen was consumed, and an equal amount of new oxygen was drawn into the circle *via* the exchanger.

A similar system for low-flow anesthesia with nitrous oxide and isoflurane is described elsewhere.[6] That system also includes an exchanger, but it does not use a computer and has considerably higher fresh-gas requirements.

Computer Algorithm

A simplified block diagram of the program is given in figure 2. The computer program worked on the assumption that the volume of xenon infused in order to decrease the oxygen concentration of the circle exponentially diluted a distribution volume composed of the circle, the lungs, and well-perfused tissues:

$$FR_{O_2} = FIN_{O_2} \cdot \exp(-V_{Xe}/V_{distr}) \quad (1)$$

where FIN_{O_2} = the initial oxygen concentration in the circle; FR_{O_2} = the resultant concentration; V_{Xe} = the volume of xenon; and V_{distr} = the distribution volume. Equation 1 yields:

$$V_{Xe} = V_{distr} \cdot \ln (FIN_{O_2}/FR_{O_2}) \quad (2)$$

When the operator decreased the desired oxygen concentration, the required amount of xenon was calculated by the computer from equation 2, assuming a distribution volume of 2 l. This volume was always less than true distribution volume. After waiting 60 s for equilibration, the resulting oxygen concentration was measured and the estimate of distribution volume was suitably revised before the next infusion of xenon. The maximum allowed change of distribution volume, from the previous value, was 50% increase or 33% decrease. A stable pattern, where oxygen concentration was within the preset hysteresis (± 2%), was achieved within 5 min. Increases in oxygen concentration were achieved by the same principle, except that oxygen was given instead of xenon:

$$V_{O_2} = V_{distr} \cdot \ln ([1 - FIN_{O_2}]/[1 - FR_{O_2}]) \quad (2')$$

where V_{O_2} = the infused volume of oxygen.

Calibrations

The volume of gas boluses infused *via* the magnetic valves was governed by varying the opening time. The relation between bolus size and opening time was established by feeding trains of identical boluses through a wet-gas meter (L1, Wohlgroth), which was used as a stan-

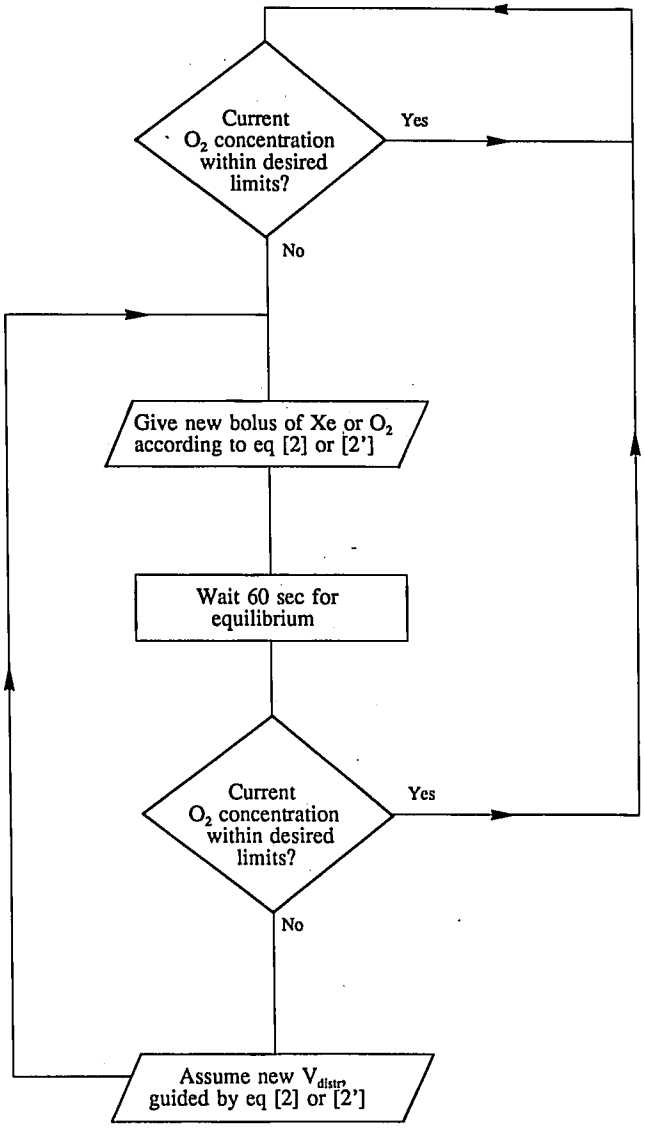

FIG. 2. Simplified block diagram of the computer algorithm. Most of the time is spent in the uppermost program loop. Eq = equation; V_{distr} = distribution volume.

dard. The oxygen analyzer was calibrated daily with 100% oxygen and with air.

Xenon Meter

The xenon meter was based on the piezoelectric sorption principle,[7] analogous to that in conventional analyzers for volatile inhalation anesthetics[8]: the xenon meter was in fact a modified Servo Gas Monitor 120 (Siemens). An oscillator quartz crystal in the analyzer was covered by a thin layer of a gas-adsorbing oil. Xenon adsorption increased the mass of the layer and changed the oscillation frequency, proportionally to the adsorbed amount. This amount, in turn, was a function of the partial pressure of xenon in the surrounding gas.

The xenon meter was calibrated against a Servomex oxygen analyzer (by the paramagnetic principle), using a mixture of pure xenon and oxygen. The effective working range for the xenon meter was 1–100% and the error ± 1%.

Experiments in Pigs

Approval was obtained from the local Animals Studies Committee. An overview of the experiment is given in table 1. Six pigs, 37–39 kg, of either sex were studied. They received azaperon, 180 mg intramuscularly, 30 min before anesthesia, which was induced with intravenous thiopental and continued with an infusion of ketamine, 6 $mg \cdot kg^{-1} \cdot h^{-1}$. The trachea was intubated orally with a cuffed tube (Portex). Relaxation was maintained with pancuronium 1 $mg \cdot kg^{-1} \cdot h^{-1}$. The tracheal tube was connected to a Siemens Servo ventilator (one separate from that of the minimal-flow system) and the lungs were ventilated with 70% air–30% oxygen at a rate of 20 breaths per min. End-tidal carbon dioxide tension, as measured with a Hewlett Packard HP472-10A in-line carbon dioxide-analyzer, was held at 35–40 mmHg. This yielded tidal volumes of 350–500 ml. A catheter was placed in a femoral or carotid artery and was connected to Hewlett Packard HP1290C pressure transducers. An infusion of 25 $g \cdot l^{-1}$ of glucose with 70 mM Na^+, 45 mM Cl^-, and 25 mM acetate was started at a rate of 120 $ml \cdot h^{-1}$. Sodium bicarbonate (0.6 M) was given as needed to maintain base deficit below 5 mM.

After about 1 h, when the preparation phase was finished, the tracheal tube was connected to the minimal-flow system. Tubing in the circle was made of silicone rubber. Denitrogenation was carried out for 20 min, by delivering 4 l of oxygen per minute *via* the magnetic valve. Xenon anesthesia was then started by setting the desired oxygen concentration at 50%. After 30 min, desired oxygen concentration was set to 30% and maintained at this level for 90 min in five pigs and for 300 min in the sixth. In the latter, desired oxygen concentration was then set to 60% for 15 min. To study the stability of the system, the computer was stopped and oxygen concentration studied with closed magnetic valves for another 7 min.

The time and size of each oxygen and xenon bolus was recorded by the computer. The total amount of xenon used was assessed by weighing the xenon bottle on a triple-beam balance (Ohaus) before and after xenon anesthesia. The cumulative amount of xenon expended, as assessed by the computer, was 0.87–1.15 (median 1.01) times the gravimetric figure. The latter was taken as "gold standard" for each pig, and the size of the boluses as estimated by the computer was multiplied by the appropriate correction factor. In three pigs, gas samples were withdrawn from the circle on one to four occasions during xenon anesthesia. The samples were taken in gas-tight 100-ml vials and were analyzed within 24 h for xenon and nitrogen content by gas chromatography. Separate tests showed that the delay in analyzing the samples did not affect the measurements. In two pigs, xenon concentration was measured in mixed gas at the outlet of the ventilator during ongoing xenon anesthesia. In this way, losses of xenon from the circle *via* the exchanger could be assessed by multiplying the concentration by the minute ventilation. Homogeneous mixing of the outlet gas was achieved with a 3-l mixing chamber.

Xenon washout was studied in four of the pigs. After 2 h of xenon anesthesia, ventilation was stopped at end-

Table 1. Overview of the Experiment: Number of Minutes for Each Phase

Pig	Preparation	Denitrogenation	Inhalation anesthesia			Washout	Inhalation anesthesia			Washout
	70% air/30% O_2	100% O_2	50% O_2		30% O_2	100% O_2	50% O_2		30% O_2	100% O_2
1	~ 60	20	30	Xe*	90	40†				
2	~ 60	20	30	Xe*	90	90†				
3	~ 60	20	30	Xe*‡	90	120†	30	N_2O	90	
4	~ 60	20	30	N_2O	90	110	30	Xe‡	90	240†
5	~ 60	20	30	N_2O	90	110	30	Xe	90	
6	~ 60	20	30	Xe	300					

* N_2 concentration in the circle studied.
† Xenon washout curve studied.
‡ Escape of Xe *via* exchanger studied.

TABLE 2. Xenon (n = 6) and Nitrous Oxide (n = 3) Expenditure during Different Periods

O_2 concentration (%) in circle →	50		30			50 for 30 min 30 for 90 min
Time interval (min) →	0–15	15–30	30–45	45–60	105–120	0–120
Xenon expenditure (l)	2.8 ± 0.3	0.6 ± 0.2	1.8 ± 0.2	0.7 ± 0.1	0.42 ± 0.1	7.6 ± 0.8
N_2O expenditure (l)	6.8 ± 0.6	1.6 ± 0.2	3.8 ± 0.4	1.3 ± 0.2	0.73 ± 0.1	16.5 ± 2.7

expiration. The tracheal tube was disconnected from the minimal-flow system and reconnected to a ventilator giving 100% oxygen in an open system. The xenon concentration in mixed expired gas was measured continuously with the prototype xenon meter. When expired xenon concentration had decreased to less than 1%, it was instead measured by gas chromatography on intermittently collected samples, in order to achieve adequate precision. The rate of xenon elimination from the pig was calculated by multiplying minute ventilation by the xenon concentration of the expired gas.

In three of the pigs, the minimal-flow system was also used for nitrous oxide anesthesia. The experimental pattern was the same as for xenon: after a 20-min denitrogenation period, desired oxygen concentration was set to 50% for 30 min, and then to 30% for 90 min. The nitrous oxide was given before the xenon in two pigs, with an intervening interval of oxygen breathing of 110 min. In the third pig, nitrous oxide was started 120 min after finishing the xenon anesthetic.

MODEL LUNG TESTS

These were carried out to investigate whether some of the xenon expenditure in the pig experiments was due to losses through the silicone rubber walls of the tubing in the circle. The model lung, which consisted of bellows placed on top of a combustion chamber fuelled with paraffin oil, consumed oxygen at a rate of 175 ml · min^{-1}. The total volume of the circle and model lung was about 3 l. In one experiment, the anesthesia circle was identical to that used in the pigs. In a control experiment, the silicone rubber tubing was replaced with polyethylene (Hytrel®) tubing. The pattern of oxygen concentration was the same as in the pigs; *i.e.*, concentration was set at 50% for 30 min and then at 30% for 90 min. Tidal volume and respiratory rate were 500 ml and 20 min^{-1}, respectively.

Results

PIGS

The operator's orders to change oxygen concentration in the circle were executed gradually by the computer program, but a stable pattern, in which the oxygen concentration varied inside allowed limits (± 2%), was usually achieved within 2.5 and always within 5 min. The volume of xenon used (at ambient temperature [20° C] and pressure [760 mmHg], dry) for a 2-h anesthetic varied between 6.7 and 9.1 l. About half of the xenon was used to achieve desired step decreases in oxygen concentration (see columns "0–15 min" and "30–45 min" in table 2), and half for maintaining oxygen concentration at the desired level. The xenon requirements for maintaining oxygen concentration at 30% gradually decreased to about 0.4 l per 15 min, *i.e.*, to about 25 ml · min^{-1} (table 2). Figure 3 shows the xenon concentration and the amount of xenon and oxygen infused into the anesthesia circle for the pig who received xenon for 6 h. Oxygen concentration in the circle decreased gradually, from 60 to 52% when the magnetic valves were closed for 7 min (fig. 3).

Nitrogen concentration in the circle as measured by gas chromatography was 12, 14, and 16% after 90–120 min of xenon anesthesia. The simultaneous figure for xenon concentration was 57, 51, and 49%, respectively.

Two minutes after setting the desired oxygen concentration to 30%, xenon concentration at the outlet of the ventilator was 940 ppm in one of the studies. This corresponded to an estimated xenon loss *via* the exchanger of approximately 9 ml · min^{-1}. The figure gradually decreased to 3 ml · min^{-1} after 8 min, and was 2 ml · min^{-1} at 22, 40, and 80 min. In the second study, xenon concentration at the outlet was less than the limit of detection (100 ppm) when measured after 95 and 120 min of xenon anesthesia, *i.e.*, during "steady-state" conditions.

Initially during washout with oxygen after the xenon anesthetic, mean expired xenon concentration decreased rapidly and was less than 5% within 2 min and less than 2% within 4 min (fig. 4). Thereafter, the decrease was more gradual. After about 60 min, the washout curve followed an approximately monoexponential course. The pattern of washout was rather similar between pigs (fig. 4). It took 5–10 min to collect the 1st l of xenon from the body, 15–20 min for the 2nd l, and about 30 min for the 3rd l. In the pig in whom washout was studied longest, about 4.4 l had been collected by 4 h. The volume remaining at this time in the pig was estimated to be 0.4 l, assuming that the tail of the washout curve was monoexponential.

The volume of nitrous oxide used (16.5 l) was about twice that of xenon (7.6 l) for a 2-h anesthetic using the

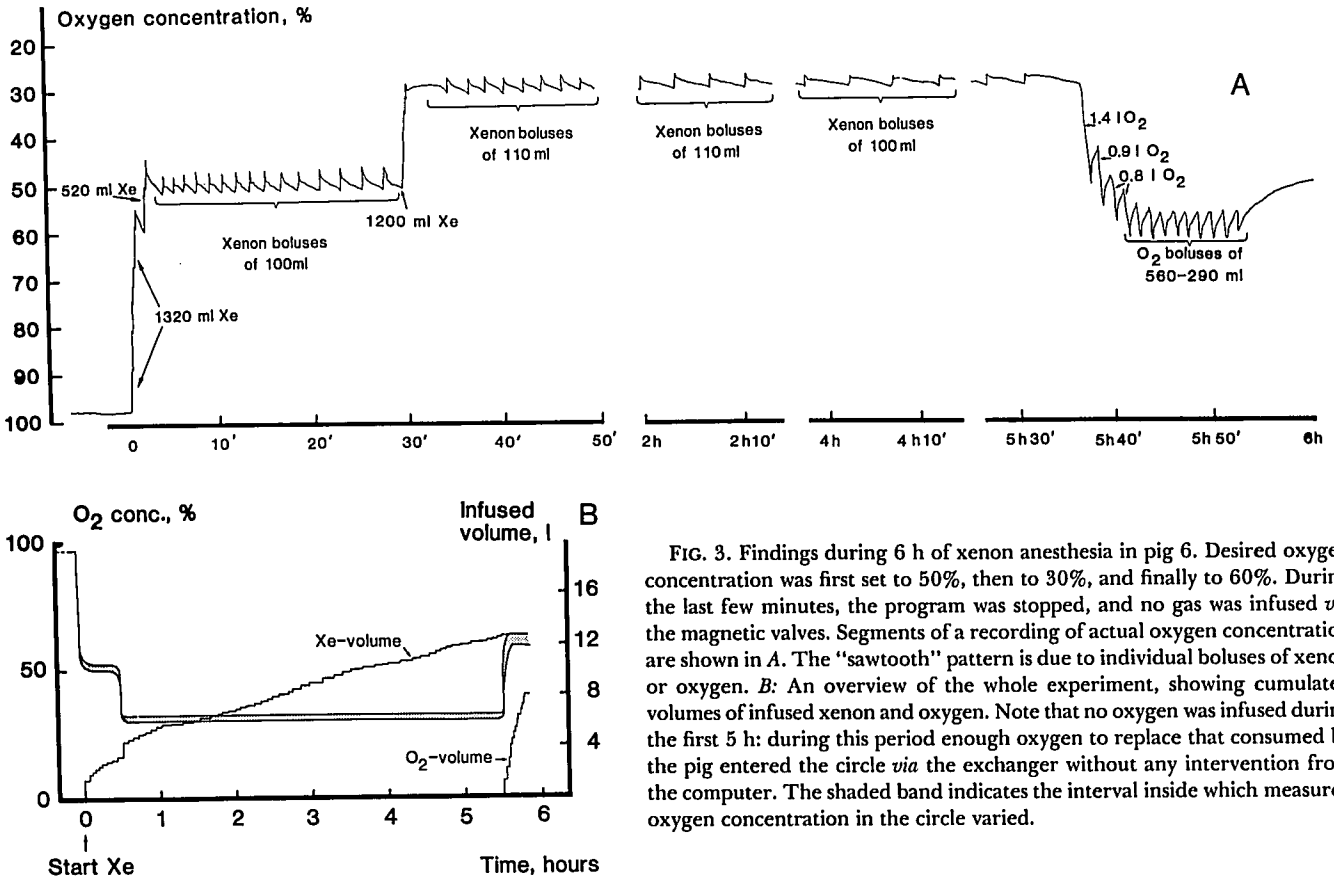

FIG. 3. Findings during 6 h of xenon anesthesia in pig 6. Desired oxygen concentration was first set to 50%, then to 30%, and finally to 60%. During the last few minutes, the program was stopped, and no gas was infused *via* the magnetic valves. Segments of a recording of actual oxygen concentration are shown in *A*. The "sawtooth" pattern is due to individual boluses of xenon or oxygen. *B:* An overview of the whole experiment, showing cumulated volumes of infused xenon and oxygen. Note that no oxygen was infused during the first 5 h: during this period enough oxygen to replace that consumed by the pig entered the circle *via* the exchanger without any intervention from the computer. The shaded band indicates the interval inside which measured oxygen concentration in the circle varied.

same pattern of oxygen concentration (table 2). Mean nitrous oxide consumption was 0.73 l during the final 15 min, as compared to 0.42 l for xenon.

Model Lung

With silicone rubber tubing, the volume of xenon infused during 2 h of simulated anesthesia was 6.9 l (at ambient temperature and pressure, dry). The mean rate of infusion during the final 15 min was 28 ml · min^{-1}. The corresponding figures with polyethylene tubing were 5.4 l and 8.5 ml · min^{-1}, respectively. The difference in expenditure (1.5 l) was considered to be due to losses from the circle into the silicone walls of the tubing.

Discussion

The great drawback of xenon is its high price ($7–15 per liter of gas), which necessitates minimal xenon consumption. One way of solving this is to use a minimal-flow system, as in the present study. However, the more the fresh gas supply in a low-flow system is decreased, the greater is the need to continuously adjust the gas supply to the circle in order to maintain the desired gas concentrations. We therefore think that an automated gas delivery system is required in order to make xenon anesthesia practicable. With a conventional circle driven by bellows or a bag, the system would have to keep track of both gas concentration and volume in the circle; the exchanger principle permits the computer program only to consider concentration. Furthermore, the exchanger made the system largely self-balancing. Figure 3 shows, for example, how 2 and ultimately 4 min passed between successive xenon boluses of 100–110 ml, during steady-state conditions. Oxygen boluses were not needed until the step increase to 60% oxygen concentration was ordered at the end of the anesthetic. However, despite possible advantages with the system there is a risk for hypoxia, should the computer or the oxygen analyzer fail. Clinical use of the system would therefore require separate monitoring of oxygen concentration with a second instrument, not involved in the computer feedback.

Although xenon has a higher potency than nitrous oxide (MAC 71 *vs.* 105%),[2,3] it is not potent enough to be used reliably as a single anesthetic in all types of patients. Some patients may not tolerate a inspired oxygen fraction of only 0.3, and even in those who do, the inspired xenon concentration cannot be increased above 1 MAC. Thus, a supplementary anesthetic would be needed in most patients.

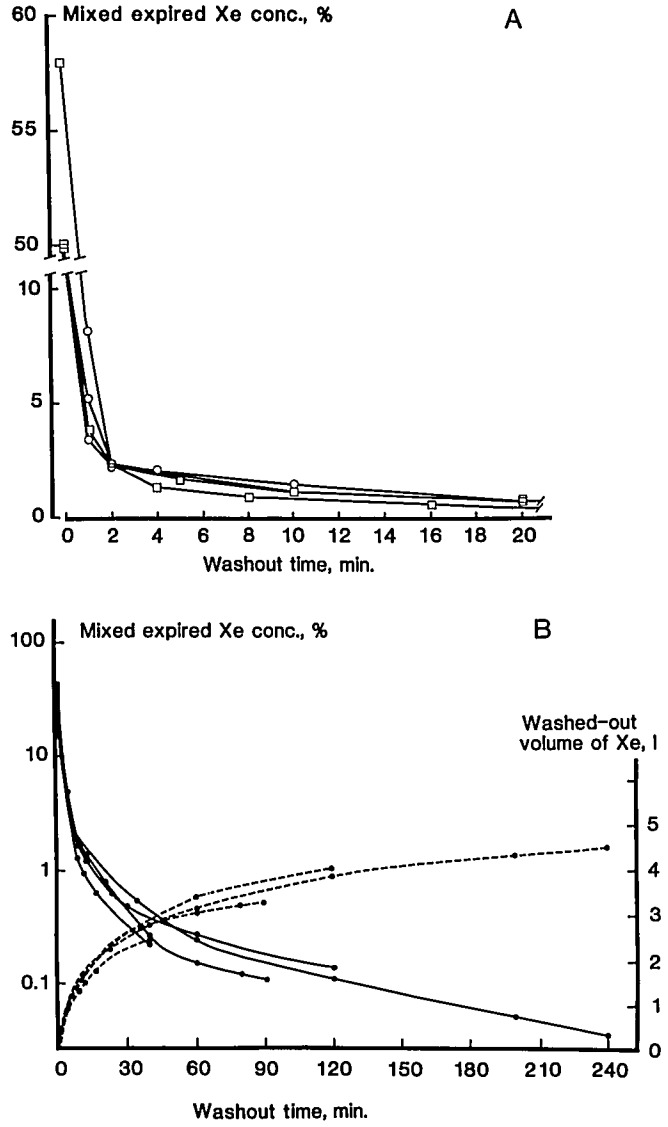

FIG. 4. Washout of xenon after the anesthetic in four pigs. *A:* Mixed expired xenon concentration during the first 20 min of washout with oxygen. Circles = xenon concentration as measured with the xenon meter; squares = xenon concentration as measured by gas chromatography. *B:* The mixed expired concentration during the whole experiment (logarithmic concentration scale) and also the cumulated washed-out volume of xenon (dashed lines).

One related problem with minimal-flow anesthesia is nitrogen accumulation. The nitrogen reduces the percentage of xenon that can be used; this may offset the advantage of its greater potency than nitrous oxide. In the present study, nitrogen concentration in the circle was 12–16% at the end of the xenon anesthesia, despite the 20 min of denitrogenation that preceded it. These figures are similar to those reported during closed-system anesthesia in humans.[9] It does not appear to be realistic to increase the period of denitrogenation further. One obvious way of removing the nitrogen is instead to increase turnover of gas in the circle, by increasing fresh gas flows, but this would increase cost. A retrieval system could be used for collecting the xenon present in the circle, and in the lungs and well-perfused organs at the end of anesthesia. However, our findings suggest that much of the xenon in the body would be eliminated only slowly: the washout curves (fig. 4) suggest that several liters remained after 5 min of washout.

Unfortunately, we used silicone rubber tubing in the circle for the experiments in pigs. According to the trials in model lungs, about 1.5 l xenon would have been saved if we had used materials impervious to xenon. Our measurements of xenon concentration at the expiratory port of the ventilator indicate that losses *via* the exchanger into the ventilator exhaust were small during "steady-state" conditions. The design of the experiment does not allow estimation of the total loss *via* this route; most of it probably occurred when the operator ordered a change in oxygen concentration. The gas infused into the circle in order to effect the change displaces xenon-containing gas from the circle into the exchanger. The exact loss would depend on how much was infused, and how fast. If the infusion is done very slowly, so that the volume expansion is offset by oxygen uptake, the losses *via* the exchanger may be negligible. Table 3, which compares the measured supply of xenon with estimated losses, suggests that somewhat more than half of the xenon was taken up by the pig, leaving about 3 l to be accounted for by other routes of expenditure.

The minimal-flow system could be valuable in experimental work using xenon, to study the mechanism of anesthetic action. For example, xenon has been used to differentiate[2] between the gas hydrate[10] and the fat solubility theories. A slightly modified version of the minimal-flow system is now used by us in clinical trials with fentanyl-supplemented xenon anesthesia.

TABLE 3. Estimated Volume (liters) of Xenon Supplied and Expended during 120 min of Minimal Flow Anesthesia

Supplied	7.6
Expended	
Lost through wall of silicone tubing according to model lung experiment	1.5
Remaining in the circle at the end of xenon anaesthesia	0.6
Washed out from the pig during 240 min of oxygen breathing after the anesthetic	4.4
Still remaining in pig after 240 min of washout	0.4
Total	6.9

Volumes at ambient temperature (20°C) and pressure (760 mmHg), dry.

Losses *via* the exchanger into the ventilator exhaust could not be estimated with precision and are not included in the table.

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References

1. Cullen SC, Gross EG: The anesthetic properties of xenon in animals and human beings with additional observations on krypton. Science 113:580–582, 1951
2. Cullen SC, Eger EI, Cullen BF, Gregory P: Observations on the anesthetic effect of the combination of xenon and halothane. ANESTHESIOLOGY 31:305–309, 1969
3. Munson ES, Saidman LJ, Eger EI II: Effect of nitrous oxide and morphine on the minimum anesthetic concentration of fluroxene. ANESTHESIOLOGY 26:134–139, 1965
4. Lachmann B, Armbruster S, Schairer W, Landstra M, Trouwborst A, van Daal G-J, Kusuma A, Erdmann W: Safety and efficacy of xenon in routine use as an inhalational anaesthetic. Lancet 335:1413–1415, 1990
5. Steward A, Allott PR, Cowles AL, Mapleson WW: Solubility coefficients for inhaled anesthetics for water, oil and biological media. Br J Anaesth 45:282–293, 1973
6. Berntman L, Luttropp HH, Werner O: Mechanical ventilation during low-flow anaesthesia. Anaesthesia 45:855–858, 1990
7. King WH: Piezoelectric sorption detector. Anal Chem 36:1735–1739, 1964
8. Kindlund A, Sundgren H, Lundström I: Quartz crystal gas monitor with a gas concentrating stage. Sensors and Actuators 6:1–17, 1984
9. Morita S, Latta W, Hambro K, Snider MT: Accumulation of methane, acetone, and nitrogen in the inspired gas during closed-circuit anesthesia. Anesth Analg 64:343–347, 1985
10. Pauling L: A molecular theory of general anesthesia. Science 134: 15–21, 1961