

The Minimum Alveolar Concentration of Xenon in the Elderly Is Sex-dependent

Takahisa Goto, M.D.,* Yoshinori Nakata, M.D., M.B.A.,† Shigeo Morita, M.D.‡

Background: The minimum alveolar concentration (MAC) of xenon in the elderly has not been determined. Moreover, because xenon inhibits the activity of the *N*-methyl-D-aspartate receptors, and because *N*-methyl-D-aspartate receptor antagonists such as ketamine and MK-801 exert sex-dependent actions, we hypothesized that the MAC of xenon would also be sex-dependent.

Methods: Forty-eight patients of both sexes (24 patients of each sex), who were aged 65 yr or older and were undergoing elective laparotomy, were anesthetized with inhalational induction of xenon. Those who demonstrated marked agitation received supplemental propofol intravenously. After tracheal intubation, the end-tidal concentration of xenon was maintained at 45 (women only), 50, 55, 60, 65, 70, or 75% (men only) for at least 15 min before skin incision. These concentrations were randomly allocated to four patients of each sex. Each patient was monitored for the presence or absence of any purposeful bodily movement for 1 min following skin incision. The MAC of xenon was calculated separately for men and women using logistic regression analysis.

Results: The MAC of xenon was 69.3% (95% CI, 63.0–75.6%) for men and 51.1% (44.6–57.6%) for women. The two 95% confidence intervals did not overlap, indicating a statistically significant difference ($P < 0.05$).

Conclusions: The MAC of xenon in the elderly is higher in men than in women.

THE gaseous anesthetic xenon has many attractive characteristics for geriatric patients. For example, its blood-gas partition coefficient is extremely low (0.12),¹ leading to fast emergence from anesthesia² regardless of the duration.³ The gas produces little cardiovascular depression.^{4,5} It also provides a good analgesic effect,⁶ thereby effectively suppressing hemodynamic⁷ and catecholamine responses⁸ to surgical stimulation.

The minimum alveolar concentration (MAC) of xenon in the elderly population has not been determined. The generally accepted value of 71% was obtained in the middle-aged population (mean \pm SD, 43 \pm 17 yr),⁹ as was the value we have recently estimated (63.1% in patients aged 45 \pm 9 yr).¹⁰

The purposes of this study were twofold. First, we sought to determine the MAC of xenon in the elderly. Second, we sought to test the hypothesis that the MAC of xenon is higher in men than in women. This hypothesis is based on the findings that (1) xenon inhibits the function of the *N*-methyl-D-aspartate (NMDA) subtype of the glutamate receptors,^{11,12} and (2) the NMDA receptor antagonists are more effective in women than in men.¹³⁻¹⁵ For example, ketamine produces a longer duration of loss of the righting reflex in female rats than in male rats,^{13,14} and this difference is greater as the animals become older.¹³ In humans, it has been observed that nitrous oxide, a potent inhibitor of NMDA receptor function,¹² produces deeper levels of anesthesia in women than in men during the initial 10 min of inhalational induction.¹⁶

Materials and Methods

Participants

After receiving approval from the Institutional Human Studies Committee of Teikyo University, Tokyo, Japan, we obtained written informed consent from 48 patients of both sexes (24 of each sex) who were aged 65 yr or older, were classified as American Society of Anesthesiologists physical status I or II, and were scheduled for elective laparotomy that required a skin incision of at least 5 cm. Exclusion criteria included history or presence of neurologic diseases, ingestion of medications known to influence anesthetic or analgesic requirements, and severe or uncontrolled medical conditions. Additional exclusion criteria included anticipated difficult airway and an oxygen saturation of arterial hemoglobin of 92% or less when measured with the pulse oximeter while the patient was breathing room air in the supine position. These criteria were applied because we needed to expose the patients to an oxygen concentration of less than 30–40% during inhalational induction of anesthesia with xenon.

Anesthesia Protocol

The anesthesia protocol was similar to that of our previous investigation,^{10,17} with some modifications. Using a computer-generated random number table, the participants were randomly allocated to a predetermined target xenon concentration of 45, 50, 55, 60, 65, 70, or 75%. Only female patients received 45% xenon, and only male patients received 75%, because we predicted that the MAC of xenon would be higher in men than in women. Therefore, six different target concen-

* Professor, † Professor and Chairman, Department of Anesthesia, Teikyo University School of Medicine. ‡ Professor, Department of Anesthesia, Teikyo University Ichihara Hospital.

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Address reprint requests to Dr. Goto: Department of Anesthesia, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo, 173-8605, Japan. Address electronic mail to: takigoto@med.teikyo-u.ac.jp. Reprints may be purchased through the Journal Web site, www.anesthesiology.org.

trations were used for each sex, and each concentration was administered to four patients of the same sex. Because the MAC-awake of xenon in the middle-aged woman is 33%,¹⁸ and 1.3–1.5 times the MAC-awake (*i.e.*, 43–50%) is necessary to assure 95% probability of unconsciousness,¹⁹ we chose 45% as the lowest concentration tested. The end-tidal concentration of xenon was continuously monitored during the study using a xenon analyzer (Anzai Medical, Tokyo, Japan).

In the operating room, anesthesia was induced in the nonpremedicated patients using inhalation of xenon in oxygen. First, the patients were preoxygenated for at least 3 min using a 10 l/min fresh flow of 100% oxygen *via* a Jackson Rees system. Then, they were instructed to take the deepest breaths possible and to exhale as much as possible. Immediately before the third inspiration, they were switched from a Jackson Rees system to the breathing circuit of an anesthesia machine (VIP-100, IMI, Saitama, Japan) that had been primed with 70% xenon in oxygen. The patients were instructed to take three additional deep breaths and subsequently were allowed to breathe as they liked while the fresh gas flows of 2 l/min xenon and 0.7 l/min oxygen were supplied. Some patients, predominantly men, became quite agitated before loss of consciousness occurred. This was manifested as vigorous head weaving and prevented us from performing inhalational induction using a face mask. In this case, 0.5 mg/kg propofol was administered intravenously. After loss of consciousness (defined as the loss of response to verbal command to open eyes), 1 mg/kg succinylcholine was administered intravenously, and the trachea was intubated following topical spray of 2.5 ml lidocaine, 4%. If the systolic blood pressure (monitored noninvasively) increased to more than 30% of the preinduction value in response to tracheal intubation, 0.5–2 mg nicardipine was administered intravenously. No patients received any medications or analgesics other than those stated.

Determination of Minimum Alveolar Concentration

The skin incision was made at least 30 min after any administration of propofol and after the xenon concentration was stable at the target end-tidal concentration for at least 15 min. Just before surgical incision, we confirmed that the patient could not respond to the verbal command to open his or her eyes. If a patient responded to the command, the response was regarded as indicating a positive somatic response to incision. Those who did not respond to verbal command were monitored for somatic response for 1 min after surgical incision by an observer who was blinded to the xenon concentration administered. As in previous studies,^{10,20} a somatic response was considered to be any purposeful bodily movement. Coughing, chewing, and swallowing were not considered to be positive purposeful movements. If the patient did not move, residual neuromus-

Table 1. Patient Demographics

	Male	Female
Age (yr)	70 ± 3	71 ± 5
Height (cm)	163 ± 7	151 ± 7
Weight (kg)	60 ± 10	52 ± 6
Smokers (n)	18*	5
Patients who received propofol during induction (n)	15*	3
Patients who received nicardipine after intubation (n)	8	6
Dose of nicardipine administered (mg)	0.9 ± 0.6	1.0 ± 0.5
Body temperature at skin incision (°C)	36.2 ± 0.1	36.1 ± 0.2

Data are mean ± SD for 24 patients of each sex. The patients who received propofol during induction showed marked agitation during induction of anesthesia with xenon inhalation. The dose of nicardipine administered is the mean for the number of patients who received it.

* $P < 0.01$, chi-square test.

cular blockade was assessed by train-of-four stimulation of the ulnar nerve. We confirmed that the height of the first twitch at skin incision was not different from that recorded before administration of succinylcholine.

Statistical Analysis

To determine the MAC value in each sex, the responses of patients to skin incision at each xenon concentration were subjected to logistic regression analysis according to the method by Waud.²¹ The demographic data were compared using unpaired *t* tests or chi-square tests as appropriate. Results are reported as mean ± SD or mean (95% CI). A *P* value < 0.05 was considered statistically significant.

Results

There were no differences between men and women with respect to age, the number of patients who received nicardipine after intubation, the dose of nicardipine administered, and the body temperature at skin incision (table 1). Significantly more male than female patients received propofol during inhalational induction of anesthesia with xenon to suppress agitation ($P < 0.001$, chi-square test).

The types of surgery performed in the participants are shown in table 2. Half (12 of 24) of the men and women underwent open prostatectomy and abdominal total hysterectomy with or without salpingo-oophorectomy. Both of these operations involved a midline skin incision of approximately 10 cm in length on the lower abdomen. Other operations were also distributed similarly between men and woman.

The MAC of xenon was 69.3% (63.0–75.6%) for men and 51.1% (44.6–57.6%) for women (fig. 1). The 95% confidence intervals did not overlap, indicating that the MACs differed significantly between the men and the women.²²

Table 2. Type of Surgery

	Male	Female
Lower abdominal		
Prostatectomy	12	NA
ATH	NA	12
Radical cystectomy	2	2
Low anterior resection	2	1
Miles	1	—
Upper abdominal		
Gastrectomy	5	3
Cholecystectomy	1	3
Right hemicolectomy	1	2
Sigmoidectomy	—	1

NA = not applicable; ATH = abdominal total hysterectomy

One female patient who received 45% xenon responded to verbal command before skin incision. All other patients of either sex failed to respond to verbal command and had skin incision during xenon anesthesia.

Discussion

We have confirmed our hypothesis that the MAC of xenon in patients aged 65 yr or older is sex dependent. It was higher in men (69%) than in women (51%). This is in marked contrast to the conventional inhalational anesthetics, because their MACs are not affected by gender, except during pregnancy.²³

Some limitations should be noted when interpreting our results. First, the observers of the patient's response

to skin incision were not blinded to the sex of the patient. Second, the skin incision was not standardized. However, table 2 suggests that the sites and lengths of skin incisions were roughly similar for men and women. Third, we used propofol when agitation occurred during inhalational induction of anesthesia with xenon. We believe that this only minimally affected our results because of the following two reasons. First, the pharmacokinetic calculation using the parameters by Schnider *et al.*²⁴ predicts that the residual concentration of propofol at the time of skin incision would have been negligible. In a male patient who is 160 cm tall and weighs 60 kg (the average values of our male patients), a 0.5-mg/kg bolus administration of propofol would produce a plasma concentration of 0.06 $\mu\text{g/ml}$ in 30 min. Because the plasma concentration associated with a 50% chance of movement to skin incision is approximately 15 $\mu\text{g/ml}$,²⁵ 0.06 $\mu\text{g/ml}$ is equivalent to 0.004 (= 0.06/15) times the MAC. Second, because more male than female patients (15 of 24 *vs.* 3 of 24) received propofol, the sex difference in the MAC would have been greater without it.

Our results are consistent with the clinical experiences reported in the literature. For example, Pittinger *et al.*²⁶ reported that all three male patients anesthetized with 75% xenon for inguinal hernia repair required supplemental meperidine, while two female patients undergoing the same operation were adequately anesthetized with xenon alone. Similarly, Morris *et al.*²⁷ reported that their only male patient, who was aged 67 yr and underwent right inguinal hernia repair, required meperidine intraoperatively to supplement general anesthesia with 75% xenon in addition to morphine and scopolamine given as premedication. Furthermore, like the majority of our male patients, this patient demonstrated marked excitement during inhalational induction with xenon. In contrast, six female patients were all adequately anesthetized with xenon alone plus premedication with scopolamine, except for occasional retching and/or emesis.

Our results may also account for the discrepancy between the MAC values reported early by Cullen *et al.*⁹ (71%) and recently by us (63%).¹⁰ While the former study did not report the numbers of male and female patients studied, approximately 80% (47 of 60) of the participants in the latter study were women. If we assume that the sex difference in the MAC we observed holds true for the middle-aged population, this alone may be sufficient to account for the discrepancy between the two studies. However, it should also be noted that Cullen *et al.*⁹ stated that their MAC value could be between 63 and 73% because of the scatter of their data.

It is not clear from our results whether the MAC of xenon in men decreases with age because the value we determined (69%) was close to those published for the middle-aged population (71% and 63% in subjects aged approximately 40 yr on average). On the other hand, it appears likely that the MAC of xenon in women de-

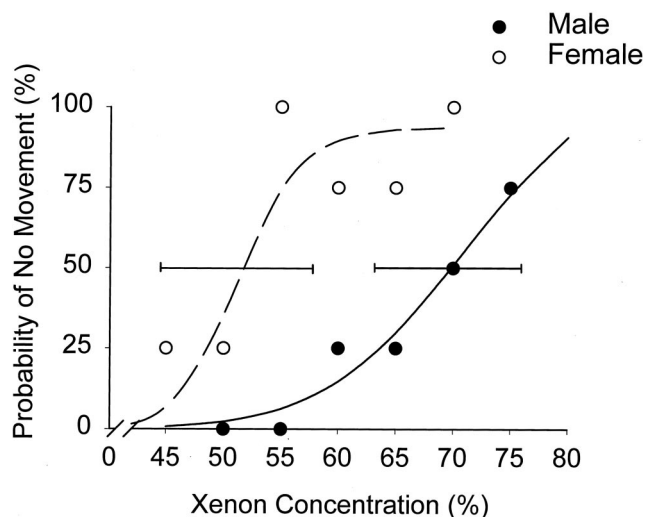


Fig. 1. The probability of no patient movement in response to skin incision is plotted against the concentration of xenon. The continuous and broken curves represent the logistic regression curves for men and women, respectively. By definition, the concentration associated with a 50% probability of no movement (the intersection between the horizontal bar and the regression curve) is the minimum alveolar concentration (MAC) of xenon for each sex. The horizontal bars represent the 95% confidence intervals of the MACs.

creases with age because it was 51% in our patients aged 65 yr or older, much smaller than the published values. For middle-aged women, reanalysis of the data on female patients in our previous study (47 patients)¹⁰ yielded a MAC of 66% at the average age of 45 yr. Using this value, the MAC at age 71 yr (the average age of the female patients in the current study) is predicted to be 56 and 55% based on the formulae by Mapleson²⁸ (MAC at age $x = \text{MAC at age } 40 \times 10^{-0.00269(x - 40)}$) and by Eger²⁹ (MAC at age $x = \text{MAC at age } 40 \times 1.32 \times 10^{-0.00303x}$), respectively. Both of these values fall within the 95% confidence interval of our result (45–58%; mean, 51%). Because these formulae are derived from the meta-analyses of published data for common volatile anesthetics (e.g., isoflurane, sevoflurane, halothane), the proximity of our result and the predicted values suggests that the MAC of xenon in women may decrease with age in a similar fashion as the MACs of common volatile anesthetics. This is interesting in light of the contrasting molecular actions of xenon and volatile agents. Xenon has little¹² or no¹¹ activity at the γ -aminobutyric acid type A receptors, whereas volatile agents markedly enhance γ -aminobutyric acid type A receptor function.

Inhalational induction of anesthesia using xenon was associated with a markedly higher incidence of agitation (62.5%) in men than in women (12.5%). This suggests that the sex difference may exist not only at the spinal level (where the MAC is predominantly mediated³⁰), but also at the supraspinal level.

In conclusion, the MAC of xenon in the elderly is sex dependent, being greater in men than in women. Whether this sex difference holds true for the younger population remains to be elucidated.

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