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Women Appear to Have the Same Minimum Alveolar Concentration as Men

A Retrospective Study

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Background: **A recent report finds that elderly Japanese women given xenon have a significantly smaller (26% less) MAC (minimum alveolar concentration required to eliminate movement in response to surgical incision in 50% of patients) than Japanese men of the same age. The authors assessed whether this finding applied to other/all anesthetics.**

Methods: **The authors reviewed data obtained previously for 258 patients (127 women and 131 men) anesthetized with desflurane, diethyl ether, halothane, methoxyflurane, sevoflurane, or xenon. Data were normalized to the MAC for the anesthetic as determined by logistic regression (*i.e.*, MAC would equal a value of 1.000.)**

Results: **The MAC for the normalized combined (all) data for women (1.013 ± 0.017; mean ± SEM) did not differ significantly from the normalized combined data for men (1.005 ± 0.009), and neither differed significantly from 1.000. However, a significantly smaller MAC value was found for women in two studies of sevoflurane (subsets of the above studies) given to Japanese patients: 12% in one study and 16% in the other.**

Conclusions: **Overall, no difference in MAC was found for women *versus* men. Whether women (particularly older Japanese women) have a smaller MAC than men remains to be confirmed by prospective studies.**

DOES gender influence the minimum alveolar concentration of an inhaled anesthetic required to eliminate movement in 50% of subjects given a noxious stimulus (MAC)? Goto *et al.*[1] used several arguments to suggest that MAC for nonpregnant women, particularly MAC for xenon, would be less than MAC for men. Consistent with their arguments, they found that the MAC for xenon for elderly women (71 ± 5 yr; mean ± SD) was 26% less than MAC for elderly men (70 ± 3 yr). The MAC values were 51.1 ± 3.2% xenon (mean ± SEM) for 24 women *versus* 69.3 ± 3.2% for 24 men ($P < 0.01$ by unpaired t test.)

Studies in animals have not demonstrated that male animals differ in their MAC from female animals that are not pregnant. Isoflurane MAC for 129J female mice did not differ from the MAC for male mice.[2] Similarly, we found (unpublished data, Edmond Eger, M.D., Michael Laster, D.V.M., James Sonner, M.D., San Francisco, California, 2001) that MAC for desflurane, halothane, and/or isoflurane does not differ in three strains of mice. Other investigators found that MAC does not differ for halothane, isoflurane, and enflurane in male *versus* female Sprague-Dawley rats and Swiss Webster mice.[3] These investigators also found that pregnant rats and mice do not have MAC values different from those of nonpregnant female rats and mice, whereas other investigators report a lower MAC in pregnant than nonpregnant rats.[4]

Chronic progesterone administration can decrease MAC[5] and induce sleep in women,[6] but Tanifuji *et al.*[7] found that MAC did not differ in women as a function of their menstrual cycle, despite large differences in plasma progesterone. Other studies demonstrate that pregnancy in some animals[4,8] and in humans,[9] including early pregnancy[10] or immediately postpartum,[11] can decrease MAC. Gender does not affect the concentration of sevoflurane or isoflurane that allows awakening (MAC_{awake}) in humans.[12]

Whether gender influences MAC, particularly in nonpregnant humans, therefore remains unclear. We thus asked whether the findings of Goto *et al.*[1] for xenon in elderly patients apply to other anesthetics. Specifically, we tested the hypothesis that MAC in men exceeds MAC in nonpregnant women.

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Materials and Methods

Data were retrieved for 258 patients (127 women and 131 men) from previous studies of MAC for desflurane and desflurane with 60% nitrous oxide,[13] diethyl ether,[14] halothane (several studies),[15,16] methoxyflurane,[14] sevoflurane (three studies),[17–19] and xenon.[15] The investigators for each of these had obtained approval for human studies as appropriate for the time period of the study. We limited the data taken from the various studies to patients who had been given 2.1 MAC or less. We also (arbitrarily) excluded data from studies in which either sex constituted less than 29% of all subjects.[20,21]

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Table 1. MAC Values for Men *versus* Women for Desflurane, Ether, Halothane, Methoxyflurane, Sevoflurane, and Xenon

			Women			Men			
Anesthetic	MAC*	MAC†	%, n	Age‡	MAC	Age‡	MAC	Ratio§	*P*
Desflurane-O_2[13]	6.00, 0.29	5.86, 0.13	42, 5	48, 7	—	48, 9	5.84, 0.23	—	—
Desflurane-N_2O[13]	2.83, 0.58	2.75, 0.75	44, 7	42, 10	2.31, 3.12	42, 10	2.59, 0.14	0.89	NS
Diethyl ether[14]	1.92	2.05, 0.11	44, 8	40, 10	2.29, 0.30	34, 14	1.94, 0.11	1.18	NS
Halothane[16]	1.08	1.11, 0.02	45, 5	0.2, 0.2	—	0.2, 0.1	—	—	—
Halothane[16]	0.91	0.92, 0.02	29, 5	4.4, 1.1	0.86, 0.05	4.1, 0.9	0.92, 0.01	0.93	NS
Halothane[16]	0.87	0.87, 0.02	50, 4	8.1, 1.3	—	8.2, 1.0	—	—	NS
Halothane[16]	0.92	0.92, 0.01	42, 5	16.4, 1.5	—	14.9, 1.9	0.92, 0.01	—	—
Halothane[16]	0.84	0.81, 0.03	57, 12	24.3, 3.6	0.83, 0.03	25.7, 2.2	0.79, 0.05	1.06	NS
Halothane[15]	0.76	0.77, 0.04	68, 17	38, 7	0.79, 0.05	50, 6	0.63, 0.36	1.25	NS
Methoxyflurane[14]	0.16	0.166, 0.012	59, 10	36, 8	0.178, 0.012	39, 10	0.147, 0.015	1.21	NS
Sevoflurane[17]	2.05, 0.08	2.05, 0.10	44, 7	36, 5	2.02, 0.22	40, 5	2.17, 0.01‖	0.93	NS
Sevoflurane[18]	1.84, 0.08	1.85, 0.08	60, 12	45, 11	1.76, 0.08	40, 12	2.10, 0.00‖	0.84	$<$0.01
Sevoflurane[19]	1.85, 0.09	1.86, 0.06	57, 20	44, 11	1.76, 0.05	37, 9	2.01, 0.09	0.88	$<$0.05
Xenon[15]	71	68.1, 4.3	33, 10	44, 19	60.5, 13.9	43, 16	71.5, 3.5	0.85	NS

* Published value, % atm; mean, SEM. † Recalculated value, % atm; mean, SEM. ‡ Average age in years, SD. § The MAC for women divided by the MAC for men. ‖ Obtained by nonlinear regression.

MAC = minimum alveolar concentration.

A MAC value for each of the anesthetics had been calculated and published by the investigators for each of the above reports (table 1). Because the methods for determination of specific MAC values varied from report to report, we recalculated the MAC value for the combined (women plus men) data for each report using logistic regression.

Then, again using logistic regression, we separately determined the MAC for women and men from each report. In a few cases, we could not determine the MAC and variance using logistic regression because the concentrations for movement did not overlap those for nonmovement. In many of these, we could determine MACs and SEMs by nonlinear regression to a sigmoid curve using an iterative Levenberg-Marquardt method with a bootstrapping approach, but in some cases, even this approach did not give reasonable values (*e.g.*, we could not separately determine the desflurane–oxygen data for women).

All data were normalized by dividing the concentration values for individual patients by the combined MAC for both women and men for that anesthetic for a given report (*e.g.*, three separate MAC values were used in the case of sevoflurane) as determined by logistic regression. We separated the data for desflurane plus 60% nitrous oxide from the remaining data and did not perform further analyses for the desflurane plus 60% nitrous oxide data because we did not wish to assume a desflurane equivalent for the nitrous oxide used. We combined the remaining normalized data for women and for men and used logistic regression to determine the MAC value (here, MAC becomes a value of 1.0, *i.e.*, a normalized value) and SEM for men and (separately) women. The difference in the MAC values for gender within a given anesthetic, and the difference in the MAC values for the combined data for each sex were compared by use of an unpaired 2-tailed Student's *t* test with no correction for multiple comparisons. We accepted $P < 0.05$ as indicating a significant difference.

Results

MAC values determined by logistic regression were virtually identical to the previously published values, differing by 0.3 ± 2.9% (mean ± SD for 14 values, table 1; no difference was statistically significant.) In 2 (both sevoflurane) of 10 comparisons, the MAC for men significantly exceeded the MAC for women. In no comparison was the value for men significantly less than the value for women. The MAC for the normalized combined (all) data for women (1.013 ± 0.017; mean ± SEM) did not differ significantly from the normalized combined data for men (1.005 ± 0.009) (fig. 1) (MAC itself would equal a value of 1.000). Considering all data except those for sevoflurane, the normalized MAC for men (0.999 ± 0.009) did not differ from that for women (1.030 ± 0.019). However, considering only the data for sevoflurane, the normalized MAC for men (1.052 ± 0.015) significantly ($P < 0.01$) exceeded the MAC for women (0.957 ± 0.025), women having a value 9% less than men.

Discussion

Overall, we found no difference in the MAC for women *versus* men. However, consistent with the report by Goto *et al.*,[1] we found two instances in which the MAC for men significantly exceeded the MAC for women (table 1). Both of these were for sevoflurane,[18,19] and both were obtained in Japanese patients. The differences between men and women found by Katoh *et al.*

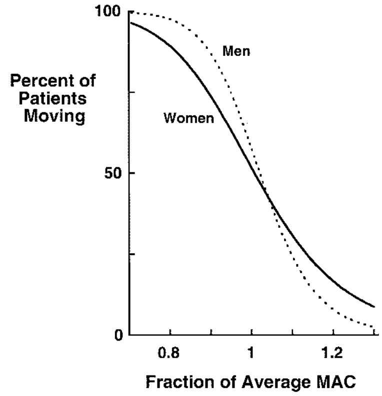

Fig. 1. The end-tidal concentrations breathed by individual patients from a given report were divided by the MAC for the anesthetic, as determined by logistic regression for the data from that report. These normalized data then were divided into those for women and those for men, and the divided data were analyzed by logistic regression. The resulting analysis shown here gave a MAC for women of 1.013 ± 0.017 (mean ± SEM) and 1.005 ± 0.009 for men (MAC itself would equal a value of 1.000; the difference between men and women was not statistically significant).

(12 and 16%)[18,19] were smaller than the difference found by Goto *et al.* (26%).[1] None of the remaining anesthetics demonstrated a significant difference, although the MAC for women given xenon by Cullen *et al.*[15] was 15% less than the MAC for men (table 1).

Overall, for six anesthetics and eight reports, we found no difference between the MAC for women and the MAC for men in a total of 258 patients (fig. 1). Thus, our findings do not support the suggestion that women generally have smaller MAC values than do men. We also do not find that younger women given xenon have a MAC significantly different from men of a similar age.

Are there subsets of patients in which women demonstrate a smaller MAC than men? Do Japanese women have smaller MAC values than Japanese men, and if such a difference exists, does it increase with increasing age? Such questions remain to be answered, but some observations suggest that the answer to both questions is that probably no difference exists. Aging should minimize or eliminate hormonal differences that otherwise might explain a difference between women and men. Many of the North American studies were done in San Francisco, where a substantial fraction of the population comes from the Far East. No obvious difference appeared in these studies, but race was not formally considered in the evaluation of the data.

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