

# Women Have the Same Desflurane Minimum Alveolar Concentration as Men

## A Prospective Study

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**Background:** Women generally report greater sensitivity to pain than do men, and healthy young women require 20% more anesthetic than healthy age-matched men to prevent movement in response to noxious electrical stimulation. In contrast, minimum alveolar concentration (MAC) for xenon is 26% less in elderly Japanese women than in elderly Japanese men. Whether anesthetic requirement is similar in men and women thus remains in dispute. The authors therefore tested the hypothesis that the desflurane concentration required to prevent movement in response to skin incision (MAC) differs between men and women.

**Methods:** Using the Dixon "up and down" method, the authors determined MAC for desflurane in 15 female and 15 male patients (18–40 yr old) undergoing surgery.

**Results:** MAC was  $6.2 \pm 0.4\%$  desflurane for women *versus*  $6.0 \pm 0.3\%$  for men ( $P = 0.31$ ), a difference of only 3%. These data provide 90% power to detect a 9% difference between the groups.

**Conclusions:** The MAC of desflurane did not differ between young men and women undergoing surgery with a true surgical incision. Although pain sensitivity may differ in women *versus* men, MAC of desflurane does not.

THE minimum alveolar concentration (MAC) is the alveolar (*i.e.*, end-tidal) concentration of an inhaled anesthetic at which 50% of patients move in response to surgical incision.<sup>1,2</sup> A key element of this definition is that skin incision is a supramaximal stimulus that fully activates pain pathways. Movement in response to skin incision is an unconscious spinal reflex.<sup>3,4</sup>

Goto *et al.*<sup>5</sup> report that xenon MAC for elderly Japanese women is 26% less than xenon MAC for elderly

Japanese men. This would seem to conflict with the finding that women experience more pain than men after comparable noxious stimuli.<sup>6–9</sup> This difference in pain sensitivity is pharmacodynamic rather than kinetic<sup>10,11</sup> and therefore implies the existence of complex, sex-based differences in the circuitry that modulates pain perception.

Consistent with increased pain sensitivity, we previously found that women required approximately 20% more desflurane than men to suppress movement in response to 100 Hz, 65- to 70-mA stimulation applied bilaterally for 10 s.<sup>12</sup> Although such electrical current is unbearable without anesthesia, it is probably not supramaximal, because anesthetic requirement as determined by this method may be less than that obtained using skin incision.<sup>13</sup> In view of these apparently conflicting data, we tested the hypothesis that MAC for desflurane in women would differ from that in men.

## Materials and Methods

In our previous study,<sup>12</sup> we found that the SD of the anesthetic requirement for desflurane was 0.5% desflurane with  $n = 10$  subjects. We thus estimated that a total of 30 patients would provide an 85% power for detecting a 10% difference in MAC between the sexes.

After obtaining approval from the Institutional Review Board and written informed consent, we enrolled 34 American Society of Anesthesiologists physical status I and II patients 18–40 yr old undergoing general anesthesia for elective surgery. We enrolled patients scheduled to have a skin incision greater than 3 cm (*e.g.*, we excluded laparoscopic procedures).

Candidates having a history of chronic pain and those taking analgesic or sedative medications were excluded, as were those having a contraindication to an inhalation induction of anesthesia. We restricted enrollment to surgeries scheduled between 8 AM and noon to minimize the circadian influence on anesthetic requirement.<sup>14</sup> We did not select patients on the basis of their menstrual cycle.

## Protocol

Patients were not given preoperative medications. Routine anesthetic monitors were applied. Anesthesia was induced by inhalation of 6–8% sevoflurane in 100% oxygen. The end-tidal concentration of the inhalational

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agent was measured with a Datex-AS-3 monitor (Datex-Engstrom, Ohmeda, Helsinki, Finland) with an accuracy of 0.1%. A neuromuscular monitor was attached to the ulnar nerve to monitor “train-of-four” response. After loss of the lash reflex, succinylcholine was given intravenously. The patients’ lungs were ventilated with 80% oxygen, the balance nitrogen, and high concentrations of desflurane until all four twitches were lost. This time was used to remove sevoflurane from the lungs and replace it with desflurane. The trachea was then intubated.

An esophageal temperature probe was inserted. Forced air was used to maintain normothermia because MAC for volatile anesthetics decreases by 4–5% per degree centigrade decrease in core temperature.<sup>15,16</sup> The patients were maintained at their assigned end-tidal desflurane concentration for at least 10 min before skin incision with a fresh-gas flow of 3 l/min. Stimulation to the patient was avoided until incision. Patients’ lungs were ventilated with a tidal volume of 5–8 ml/kg. Before skin incision, we confirmed that the patient had recovered four full twitches in response to supramaximal stimulation of the ulnar nerve at the wrist and that residual sevoflurane concentration was <0.1%. The first male and female patients studied were assigned to an end-tidal desflurane concentration of 6%. If this patient moved in response to surgical skin incision, the concentration was increased by 0.5% desflurane in the subsequent patient of that sex. In contrast, the desflurane concentration in the subsequent patient in that group was decreased by 0.5% if skin incision did not provoke movement. This paradigm is referred to as the “Dixon up-and-down” method.<sup>17</sup>

### Measurements

Two independent investigators blinded to the end-tidal concentration of desflurane determined patient response to skin incision (movement or no movement). One investigator observed the upper extremities and head of the patient, and the other investigator observed the lower extremities. A positive response to skin incision was defined by a purposeful movement of one or more extremities or the head.<sup>3</sup> Grimacing and coughing were not considered purposeful responses. Patients were observed for movement for 1 min after skin incision.

### Data Analysis

Our primary outcome was MAC, defined as the concentration of desflurane required to prevent movement in 50% of patients in response to skin incision. MAC was calculated as the average desflurane in each group for independent pairs of patients in which one patient moved and the next did not.

Results in men and women were compared by unpaired Student’s *t* test. Data are presented as mean  $\pm$  SD;

**Table 1. Characteristics of Patients and Potential Confounding Factors**

	Women (n = 15)	Men (n = 15)	P
Height, cm	163 $\pm$ 7	179 $\pm$ 9	<0.001
BMI, kg/m <sup>2</sup>	30 $\pm$ 8	27 $\pm$ 5	0.32
Age, yr	33 $\pm$ 9	27 $\pm$ 8	0.10
Time from induction to incision, min	24 $\pm$ 7	23 $\pm$ 10	0.91
Core temperature, °C	36.3 $\pm$ 0.5	36.1 $\pm$ 0.4	0.31
Heart rate, bpm	90 $\pm$ 19	97 $\pm$ 17	0.33
Systolic pressure, mmHg	112 $\pm$ 15	121 $\pm$ 13	0.10
Diastolic pressure, mmHg	69 $\pm$ 10	73 $\pm$ 12	0.25

Values below the line were obtained at the time of skin incision. Data are presented as mean  $\pm$  SD. BMI = body mass index; bpm = beats per minute.

a value of  $P < 0.05$  was considered statistically significant. We considered differences in anesthetic requirement differing by less than 10% to be clinically unimportant.

## Results

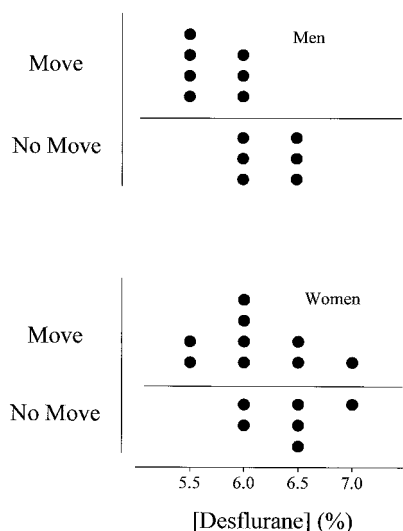
We enrolled 17 male and 17 female patients in the study. Data from two men and two women were deleted because of protocol violations: incision was made before the end of an adequate (10-min) equilibration period in three patients, and opioid was inadvertently given before the incision in one patient. Analysis was thus restricted to the data obtained from the remaining 30 patients.

Demographic and morphometric characteristics did not differ between groups except for height, which was greater for men (table 1). We had data on the menstrual cycle phases of 10 of the 15 women: these were equally divided between premenstrual, periovulatory, and luteal phases of menstruation. The average time from induction of anesthesia to incision was 24 min in each group, which allowed us to maintain steady end-tidal desflurane concentrations for at least 10 min before incision. Core temperature and hemodynamic responses were similar in each group at the time of incision.

The average desflurane concentration required to prevent movement in 50% of the patients did not differ between women and men (fig. 1). The MAC of desflurane was  $6.2 \pm 0.4\%$  in women and  $6.0 \pm 0.3\%$  in men ( $P = 0.31$ ), a difference of 3%. These data provide 85% power to detect a 10% difference between the groups.

## Discussion

Estrogen and progesterone play a pivotal role in establishing the pain threshold during pregnancy and parturition,<sup>18–20</sup> perhaps because female sex hormones modulate neuronal excitability *via* effects on the ion



**Fig. 1.** The end-tidal concentrations of desflurane tested in men and women. Points above the horizontal lines indicate movement (*Move*), whereas those below the lines indicate no movement (*No Move*). MAC for desflurane in men was  $6.0 \pm 0.3\%$ ; in women, it was  $6.2 \pm 0.4\%$ ,  $P = 0.31$  (mean  $\pm$  SD).

channels responsible for spinal and supraspinal neurotransmission.<sup>21,22</sup> It is therefore unsurprising that there appear to be sex differences in endogenous pain-inhibitory circuitry in men and women. For example, women report both temporary and persistent pain more frequently than men<sup>8</sup> and report greater pain in response to a given stimulus.<sup>7,9,23–25</sup>

The results of previous work from this laboratory found that women required 20% more desflurane than men to block reflex movement in response to electrical stimulation.<sup>12</sup> However, desflurane MAC did not differ in the male and female participants in the present study. MAC values in both cases were approximately 6%, a value similar to that previously reported for patients of this age.<sup>26</sup> These present results have a high degree of statistical power, indicating that there is less than a 10% chance that anesthetic requirements in men and women differ by more than 9%. It is thus unlikely that we simply failed to detect a true sex difference in MAC. Instead, differences between our previous and current protocols presumably explain the contrasting results.

The critical difference appears to be that Greif *et al.*<sup>12</sup> used tetanic electrical shocks as the noxious stimulus rather than surgical skin incision. Although tetanic current at 65 mA is unbearable without anesthesia, anesthetic requirement, as determined by this method, is consistently less than that obtained by formal MAC testing.<sup>13</sup> For example, the average desflurane requirement in the study by Greif *et al.* was 5%, whereas it was 6% in the present study, a difference of 20%. The key distinction here is that skin incision is a supramaximal stimulus that fully activates pain receptors and pathways. Electrical stimulation is not, and therefore, it provides graded activation of pain pathways.

It is worth noting, however, that there is little evidence that pain pathways are interrupted by volatile anesthetics. For example, MAC-BAR (MAC of inhalation agent that blocks adrenergic responses to skin incision) considerably exceeds MAC.<sup>27</sup> Furthermore, small concentrations of opioids substantially decrease MAC. And finally, the increase in ventilation prompted by skin incision is similar with either 1 or 2 MACs of isoflurane or halothane anesthesia.<sup>28</sup> We must thus consider the possibility that our previous results are wrong.<sup>12</sup>

It remains unclear why our results differ so markedly from those reported recently by Goto *et al.*<sup>5</sup> in which elderly Japanese women were found to require 26% less xenon than elderly Japanese men. Possibly the effects of xenon and desflurane on anesthetic requirement for men and women are dissimilar. Alternatively, there may be a sex difference for Japanese women *versus* men but not for Caucasian women *versus* men. Age-related pharmacokinetic differences could also account for the discrepancy.<sup>26,29,30</sup> MAC for inhalation anesthetics consistently decreases with age<sup>26</sup>; this age-related change could be different in men than women, because hormonal levels probably affect the efficacy of inhalation anesthetics. For example, women in early pregnancy have a decreased MAC for isoflurane, halothane, and enflurane compared with nonpregnant women.<sup>31</sup> Thus, the altered hormonal milieu in the postmenopausal women may alter the response to inhalation anesthesia as well.

The pain threshold varies as a function of the menstrual cycle.<sup>32</sup> Women have a higher pain threshold in the follicular phase than in the periovulatory, luteal, or premenstrual phases. Women are most sensitive to ischemic, thermal, and pressure pain during the luteal phase.<sup>33,34</sup> It is thus a limitation of our study that we included women in all phases of their menstrual cycles. Doing so may have increased response variability in the women. Nonetheless, the SD in the women was relatively small, and the study was well powered to detect even small differences in anesthetic requirement. There remains a 10% chance that anesthetic requirements in men and women differ by as much as 9%. However, such small differences are of little clinical or physiologic importance. Finally, the work of Tanifuji *et al.*<sup>35</sup> suggests that the phase of the menstrual cycle is irrelevant to MAC, despite its effect on the perception of pain.

In summary, the MAC of desflurane did not differ in young, healthy men and women. This result contrasts with previous results in which anesthetic requirement was based on the response to electrical stimulation. It also differs from studies showing that women report more pain than men. We thus conclude that although pain sensitivity is augmented in women, anesthetic requirement may not be.



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