

Effect of N₂O on Sevoflurane Vaporizer Settings during Minimal- and Low-flow Anesthesia

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Background: Uptake of a second gas of a delivered gas mixture decreases the amount of carrier gas and potent inhaled anesthetic leaving the circle system through the pop-off valve. The authors hypothesized that the vaporizer settings required to maintain constant end-expired sevoflurane concentration (Et_{sevo}) during minimal-flow anesthesia (MFA, fresh gas flow of 0.5 l/min) or low-flow anesthesia (LFA, fresh gas flow of 1 l/min) would be lower when sevoflurane is used in oxygen-nitrous oxide than in oxygen.

Methods: Fifty-six patients receiving general anesthesia were randomly assigned to one of four groups (n = 14 each), depending on the carrier gas and fresh gas flow used: group Ox.5 l (oxygen, MFA), group NOx.5 l (oxygen-nitrous oxide, MFA after 10 min high fresh gas flow), group Ox1 l (oxygen, LFA), and group NOx1 l (oxygen-nitrous oxide, LFA after 10 min high fresh gas flow). The vaporizer dial settings required to maintain Et_{sevo} at 1.3% were compared between groups.

Results: Vaporizer settings were higher in group Ox.5 l than in groups NOx.5 l, Ox1 l, and NOx1 l; vaporizer settings were higher in group NOx.5 l than in group NOx1 l between 23 and 47 min, and vaporizer settings did not differ between groups Ox1 l and NOx1 l.

Conclusions: When using oxygen-nitrous oxide as the carrier gas, less gas and vapor are wasted through the pop-off valve than when 100% oxygen is used. During MFA with an oxygen-nitrous oxide mixture, when almost all of the delivered oxygen and nitrous oxide is taken up by the patient, the vaporizer dial setting required to maintain a constant Et_{sevo} is lower than when 100% oxygen is used. With higher fresh gas flows (LFA), this effect of nitrous oxide becomes insignificant, presumably because the proportion of excess gas leaving the pop-off valve relative to the amount taken up by the patient increases. However, other unexplored factors affecting gas kinetics in a circle system may contribute to our observations.

MINIMAL-FLOW anesthesia (MFA) and low-flow anesthesia (LFA) techniques use fresh gas flows of 0.5 and 1 l/min, respectively.¹ However, these definitions ignore the effect of carrier gas composition on the amount of gas wasted through the pop-off valve. Because uptake of a second gas (oxygen being the first gas) decreases the amount of carrier gas and potent inhaled anesthetic

leaving through the pop-off valve, we hypothesized that the vaporizer setting required to maintain a constant end-expired sevoflurane concentration (Et_{sevo}) during MFA or LFA would be lower when sevoflurane is used in oxygen-nitrous oxide than in oxygen.

Materials and Methods

After obtaining Institutional Review Board approval and written informed consent from each patient, 56 patients, American Society of Anesthesiologists (ASA) physical status I or II, scheduled to undergo a variety of surgical procedures on an extremity were enrolled. The patients were randomly assigned to one of four groups (n = 14 each), depending on fresh gas flow management. After preoxygenation (oxygen fresh gas flow 8 l/min) for 3 min, propofol, 3 mg/kg, cisatracurium, 0.15 mg/kg, and sufentanil, 0.1 µg/kg, were administered intravenously. After tracheal intubation, oxygen fresh gas flow in group Ox.5 l was lowered to 0.5 l/min. In group NOx.5 l, a high fresh gas flow (2 l/min oxygen and 4 l/min nitrous oxide) was used for 10 min to account for the high initial nitrous oxide requirements;² thereafter, a total fresh gas flow of 0.5 l/min was used, with the relative proportion of oxygen and nitrous oxide titrated to maintain the inspired oxygen fraction (F_{iO_2}) between 0.28 and 0.32. In group Ox1 l, 1 l/min oxygen was used throughout the study after intubation. In group NOx1 l, fresh gas flow management was similar to group NOx.5 l, but total fresh gas flow (oxygen and nitrous oxide combined) after 10 min was 1 l/min. In all groups, the sevoflurane vaporizer dial was initially set at 8% to rapidly attain an Et_{sevo} of 1.3%; as soon as the Et_{sevo} was 1.3%, the vaporizer dial setting was adjusted to maintain the Et_{sevo} at 1.3%. Vaporizer dial settings were recorded every minute but are presented only every 2 min. When signs of light anesthesia developed, an additional bolus of sufentanil, 0.1 µg/kg, was administered. Light anesthesia was defined as tachycardia (heart rate [HR] > 125% of preinduction values or HR > 110 beats/min) or hypertension (mean arterial pressure [MAP] > 125% of preinduction values or MAP > 100 mmHg). Hypotension (MAP < 75% of preinduction values or MAP < 60 mmHg) and bradycardia (HR < 50 beats/min) were treated with 5 mg of ephedrine or 0.5 mg of atropine, respectively.

Because the reproducibility of our data is contingent on the use of equipment with similar performance characteristics and the same circle system configuration as

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Table 1. Patient Demographics

	Group Ox.5L O ₂ 0.5 l/min	Group NOx.5L O ₂ /N ₂ O 0.5 l/min	Group Ox1L O ₂ 1 l/min	Group NOx1L O ₂ /N ₂ O 1 l/min
Age (yr)	56 ± 14	55 ± 20	51 ± 19	55 ± 13
Height (cm)	170 ± 5	159 ± 26	170 ± 6	170 ± 11
Weight (kg)	74 ± 18	73 ± 30	75 ± 18	79 ± 13

Results are mean ± SD. N = 14 in each group. There are no differences among groups.

the one used in this study, an accurate description is needed. The vapor concentration output of the ADU vaporizing unit (ADU anesthesia workstation, Datex-Ohmeda, Helsinki, Finland) can be increased with 0.1% increments. All data were collected using one ADU anesthesia workstation with one vaporizing (Aladin[®]) cassette in the same operating room with the same agent analyzer. The vaporizer in the ADU compensates for the carrier gas composition by adjusting the cassette flow based on proprietary algorithms. We tested the accuracy of this specific vaporizer and anesthesia workstation: with a fresh gas flow of 0.5 l/min oxygen, 0.5 l/min nitrous oxide–oxygen, 1 l/min oxygen, 1 l/min nitrous oxide–oxygen, and 5 l/min nitrous oxide–oxygen, vaporizer output with dial settings of 2 and 4% were 2.0, 1.9, 2.0, 2.0, 2.0% and 4.1, 4.0, 4.1, 4.0, 4.2%, respectively, as determined by the same agent analyzer used in the study. The performance of this particular vaporizer remained therefore within the previously described accuracy of this type of vaporizer (Aladin[®] cassette).³ Inspired and expired gases were analyzed by an agent analyzer (Datex-Engstrom Compact Airway Module M-CAiOV, Datex-Engstrom, Helsinki, Finland; accuracy for sevoflurane ± 0.2%) and downloaded in a spreadsheet every minute. Gases sampled by the agent analyzer were redirected to the expiratory limb of the anesthesia circuit to allow the use of 0.5 l/min fresh gas flow with nitrous oxide–oxygen. In addition, 100% oxygen was used instead of air as the reference gas for the paramagnetic oxygen analyzer to attenuate N₂ accumulation.⁴

Patients' lungs were mechanically ventilated with tidal volumes of 8 ml/kg and a respiratory rate of 10 breaths/min. Because the circle system configuration influences the gas flow characteristics in the circle system, a precise description is needed.⁵ The Datex-Ohmeda Compact Block (Helsinki, Finland) was used, a patented part of the circle system containing inspiratory and expiratory valves, fresh gas flow connection, and a small disposable canister containing sodalime. Fresh gas flows continuously into the inspiratory limb (during inspiration and expiration) at a site located between the inspiratory unidirectional valve and the patient. The tidal volume delivered by the anesthesia ventilator is compensated for this effect of fresh gas flow. The tube that connects the ventilator to the circle system is positioned between the exhalation unidirectional valve and the absorber. Excess gas is scavenged from within the bellows housing

through the bellows block overflow valve (= ventilator pressure relief valve). The volume of the circle system is 3.4 l. The leak of the anesthesia machine and circuit during controlled mechanical ventilation with a peak-inspiratory pressure of 30 cm H₂O was measured each morning by the system check leak test. The actual leak for each patient during the study period was calculated based on the system check leak test and the measured peak-inspiratory pressure and inspired-to-expired ratio, and ranged from 9 to 27 ml/min, assuming a first order (linear) leak.

Statistical Analysis

Patient demographics and vaporizer settings after the 10-min equilibration period following tracheal intubation were analyzed using analysis of variance (ANOVA) followed by Student–Newman–Keuls test. *P* < 0.05 was considered statistically significant.

Results

Patient demographics did not differ among groups (table 1). None of the patients had episodes of hypotension, hypertension, bradycardia, or tachycardia that required treatment. Et_{sevo} reached 1.3% within 5, 1, 2, and 1 min in all patients in groups Ox.5 l, NOx.5 l, Ox1 l, and NOx1 l, respectively, and oscillated briefly around the target value (fig. 1). These oscillations were more pronounced in the groups in which high fresh gas flows were used initially (groups NOx.5 l and NOx1 l). Thereafter, Et_{sevo} remained within 0.1% of the desired Et_{sevo} (fig. 1). After 10 min of controlled mechanical ventilation, the end-expired carbon dioxide values remained constant in all patients during the study period; the mean end-expired P_{CO₂} ranged between 33 and 38 mmHg.

In group Ox.5 l, the vaporizer dial settings were gradually decreased during the first 20 min of the study and were stable thereafter. The vaporizer settings in group Ox.5 l were higher than in the other three groups from 2 min on until the end of the study (fig. 2). In group Ox1 l, vaporizer dial settings were also gradually decreased during the first 20 min of the study and were stable thereafter. In groups NOx.5 l and NOx1 l, vaporizer settings required readjustments after the 10 min of high fresh gas flow but stabilized within the next 10 min. Vaporizer settings after the initial 10-min high fresh gas

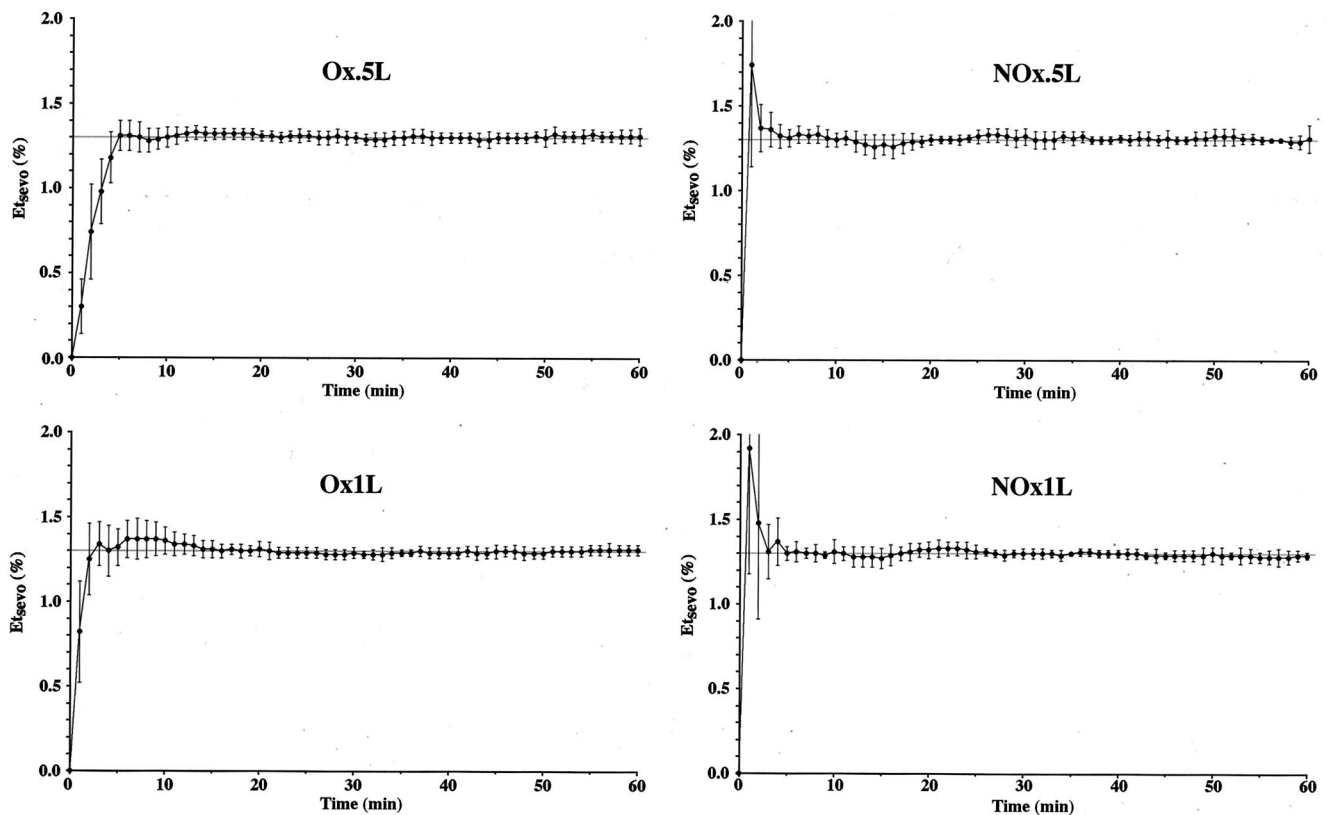


Fig. 1. Sevoflurane end-expired concentrations ($E_{t_{sevo}}$) in the four groups.

flow period after tracheal intubation were higher in group NOx.5 l than in group NOx1 l between 23 and 47 min ($P < 0.05$). Vaporizer settings were not different between groups Ox1 l and NOx1 l ($P > 0.05$).

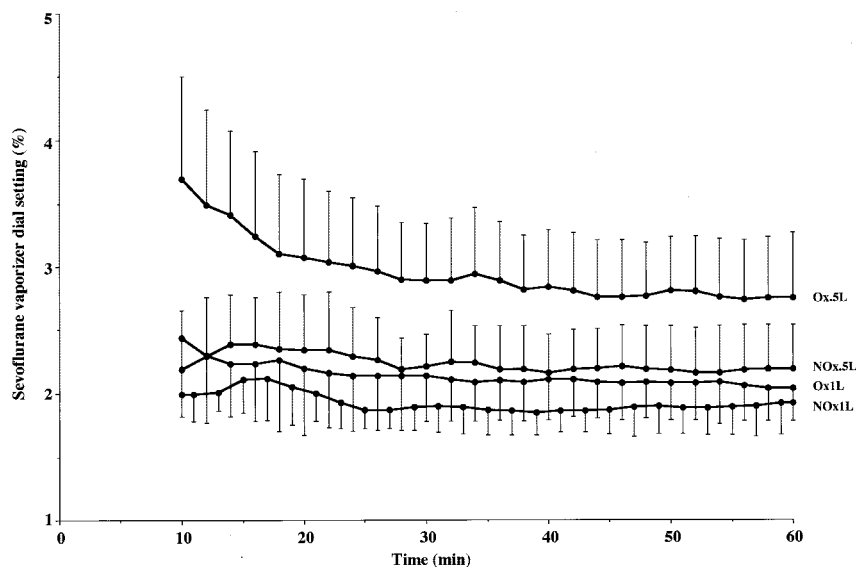
Discussion

After an initial high fresh gas flow period to ensure rapid wash-in and to account for the initially high nitrous oxide requirements, the vaporizer setting required to maintain a constant $E_{t_{sevo}}$ during MFA (fresh gas flow of 0.5 l/min) is markedly lower when sevoflurane is administered in an oxygen-nitrous oxide mixture compared with when only oxygen is used. This effect is insignificant during LFA (fresh gas flow of 1 l/min).

Two factors affecting the pharmacokinetics of gases and vapors in a circle system may explain these findings. First, when nitrous oxide is used, more carrier gas is taken up by the patient, and less gas and vapor will leave the circle system through the bellows block overflow valve. As a result, the vaporizer dial setting required to maintain a constant $E_{t_{sevo}}$ is lower when nitrous oxide is used (compare group Ox.5 l vs. NOx.5 l). Second, because there is more rebreathing with a lower fresh gas flow, more exhaled gas (with the lower expired concentration resulting from uptake by the patient) will dilute

the fresh gas concentration to produce a reduced concentration of the vapor in the inspired gas. Consequently, the vaporizer dial setting will have to be higher to maintain the same inspired and alveolar (end-expired) concentrations. This phenomenon explains the differences between groups Ox.5 l and Ox1 l and between groups NOx.5 l and NOx1 l. The effect of both phenomena on the vaporizer dial setting required to maintain $E_{t_{sevo}}$ constant apparently becomes insignificant with higher fresh gas flows (in this study 1 l/min): when the amount of gas and vapor lost through the bellows block overflow valve relative to the amount taken up by the patient increases, the effect of nitrous oxide and sevoflurane uptake on vaporizer dial setting decreases. Above a certain fresh gas flow, vaporizer dial settings required to maintain a constant $E_{t_{sevo}}$ remain virtually the same. This phenomenon explains the absence of a difference between groups Ox1 l and NOx1 l. These two factors can largely explain our findings from this study, as illustrated by calculations based on recently acquired clinical update data (see Appendix).⁶⁻⁹ When the amount of sevoflurane taken up by the patient, the amount of sevoflurane wasted through the bellows block overflow valve, and total fresh gas flow are known, the sevoflurane vaporizer dial setting required to maintain $E_{t_{sevo}}$ at 1.3% can be accurately predicted. Sevoflurane uptake at

Fig. 2. Sevoflurane vaporizer dial setting (mean \pm SD, %) required to attain and to maintain the end-expired concentration at 1.3%. See text for results and statistical significance of any differences.



1.3% Et_{sevo} remains approximately constant at 10.5 ml vapor/min between 15 and 45 min. We can calculate that approximately 3.25, 0, 9.75, and 6.5 ml of sevoflurane vapor leaves the circle system through the bellows block overflow valve per minute in groups Ox.5 l, NOx.5 l, Ox1 l, and NOx1 l, respectively, if we assume that (1) the concentration of sevoflurane in the scavenged gas is 1.3%; (2) both oxygen consumption and nitrous oxide uptake (after 15 min) are 250 ml/min;^{2,8-10} and (3) the amount of carrier gas in excess of patient uptake is 250, 0, 750 and 500 ml/min in groups Ox.5 l, NOx.5 l, Ox1 l, and NOx1 l, respectively. Under these conditions, the sevoflurane vaporizer dial settings required to maintain Et_{sevo} at 1.3% are calculated to be 2.8, 2.1, 2.0, and 1.7% in groups Ox.5 l, NOx.5 l, Ox1 l, and NOx1 l, respectively. Sevoflurane use between 15 and 55 min is 630, 472.5, 900, and 765 ml of vapor in groups Ox.5 l, NOx.5 l, Ox1 l, and NOx1 l, respectively. Discrepancies between these calculations for vaporizer settings and the results seen in our patients can, in part, be explained by differences in sevoflurane, oxygen, and nitrous oxide uptake (which, however, were not measured), or inadequate power of the study (too few patients), or a difference in anesthetic depth when using nitrous oxide (0.6 MAC) possibly resulting in changes in hemodynamics, tissue perfusion, and tissue uptake of sevoflurane.

The second gas effect of nitrous oxide on sevoflurane may also have contributed to our observations.¹¹ Because the Et_{sevo} was maintained constant in this study, the second gas effect would be expected to lead to lower vaporizer dial settings in the groups in which nitrous oxide was used. The clinical importance of the second gas effect, however, is controversial, as highlighted by two recent manuscripts with opposing conclusions.^{12,13} Its effect in our study was probably small (in the 1-l/min groups, there was no difference in vaporizer dial settings) and certainly cannot be the only ex-

planation given the large difference between the two 0.5-l/min groups. Nevertheless, because the second gas effect does affect inspired and expired volumes and concentrations, it may have affected the vaporizer dial settings in this study.

Not only is there a second gas effect, Lowe also mentions a reverse fourth and fifth gas effect resulting from elimination of carbon dioxide and H₂O, respectively.¹⁴ These are two of the factors contained in the so-called "general anesthetic equation," a theoretical framework developed by Lowe and Ernst to predict vaporizer dial settings required to attain and maintain a constant end-expired concentration in a circle system with any fresh gas flow if the following are known: uptake of oxygen, nitrous oxide, and the potent inhaled anesthetic; H₂O and carbon dioxide production; dead space and alveolar minute ventilation; and leaks of the system.¹⁰ To completely and accurately quantitate all these factors affecting gas kinetics in a circle system, a more complex clinical setup than used in this study would be needed, including a modification to allow the measurement of gas volumes and concentrations leaving the circle system through the pop-off valve.

The terminology regarding the classification of fresh gas flows is confusing. The current definitions of minimal- and low-flow anesthesia techniques (MFA and LFA) are the use of fresh gas flows of 0.5 and 1 l/min, respectively.¹ These definitions have been pioneered by authors such as Virtue.¹⁵ Unfortunately, others did not follow these definitions, which has resulted in significant confusion. In addition, Eger recently defined "low inflow administration" as a fresh gas flow of less than half the minute volume (usually less than 3 l/min), and "high inflow rates" as 5 l/min or greater.¹¹ Regrettably, this definition does not differentiate between fresh gas flows below 3 l/min. The issue becomes even more confusing when the actual uptake of gases and vapors by the

patient are considered. Whereas 250 ml/min of oxygen would constitute closed circuit anesthesia for a large adult, this is far in excess of oxygen consumption by an infant. In addition, our results suggest that definitions of low-flow techniques have to consider the effect of carrier gas composition. Because a range of fresh gas flows and a variety of gas mixtures can be used (oxygen, oxygen-nitrous oxide, oxygen-air, oxygen-xenon), we suggest that one should always refer to the flow of each carrier gas rather than trying to come to a uniform definition.

We conclude that during MFA (0.5 l/min), the vaporizer dial setting required to maintain $E_{t_{sevo}}$ constant at 1.3% is lower when sevoflurane is delivered in an oxygen-nitrous oxide mixture than in oxygen alone because less gas and vapor are wasted through the pop-off valve with the oxygen-nitrous oxide mixture. During LFA (1 l/min), however, vaporizer dial settings are similar with oxygen-nitrous oxide or oxygen, presumably because the proportion of excess gas leaving the pop-off valve relative to the amount taken up by the patient increases. However, other unexplored factors affecting gas kinetics in a circle system may contribute to our observations. Definitions of low-flow techniques have to consider the effect of the carrier gas composition on the gas kinetics in the circle system.

Appendix

Table 2. Calculations Illustrating Sevoflurane Vaporizer Dial Settings Required to Maintain 1.3% End-expired Sevoflurane during Minimal-flow and Low-flow Anesthesia with or without nitrous oxide

Group	Carrier Gas Composition	FGF l/min	FGF in excess of V_{O_2} and $V_{N_2O}^{a,b}$ l/min	Sevo loss (scavenged) ^c ml vapor/min	V_{Sevo}^d ml vapor/min	Vap % ^e %	Sevo vaporized ^f ml vapor/15–55 min interval
Ox.5L	O ₂	0.5	250	3.25	10.5	2.8	561
NOx.5L	O ₂ /N ₂ O	0.5	0	0	10.5	2.1	420
Ox1L	O ₂	1	750	9.75	10.5	2.0	799
NOx1L	O ₂ /N ₂ O	1	500	6.5	10.5	1.7	680

FGF = fresh gas flow; V_{O_2} = oxygen consumption; V_{N_2O} = nitrous oxide uptake; Sevo = sevoflurane; V_{sevo} = sevoflurane uptake by the patient; Vap% = vaporizer dial setting.

(a) Oxygen consumption is approximately 250 ml/min.¹⁰

(b) Nitrous oxide requirements to attain an end-expired concentration of 60–65% are high the first few minutes because of circuit and lung wash-in but then gradually decrease to 250 ml/min after 10 min. These nitrous oxide requirements have been mathematically expressed as $1000 \cdot t^{-1/2}$ ml/min.³

(c) Assumes that the concentration of sevoflurane in the scavenged gas is 1.3%. In reality, it may be slightly higher (between inspired and expired concentrations).

(d) Sevoflurane uptake (vapor) after 15 min remains approximately constant at 10.5 ml/min during the ensuing 45 min ($E_{t_{sevo}}$, 1.3%).

(e) Calculated as (ml sevoflurane lost through bellows block overflow valve + ml sevoflurane taken up by the patient)/total FGF.

(f) Calculated in each group from the dialed-in concentration at the common gas outlet and FGF.

The vaporization effect (sevoflurane vapor is added to carrier gas, thereby increasing total fresh gas flow) is ignored because it is not mathematically significant.

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