

In Vitro *Compound A Formation in a Computer-controlled Closed-circuit Anesthetic Apparatus*

Comparison with a Classical Valve Circuit

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Background: **Few data exist on compound A during sevoflurane anesthesia when using closed-circuit conditions and sodalime with modern computer-controlled liquid injection.**

Methods: **A PhysioFlex apparatus (Dräger, Lübeck, Germany) was connected to an artificial test lung (inflow ≈ 160 ml/min carbon dioxide, outflow ≈ 200 ml/min, simulating oxygen consumption). Ventilation was set to obtain an end-tidal carbon dioxide partial pressure (P_{ETCO_2}) ≈ 40 mmHg. Canister inflow ($T°_{in}$) and outflow ($T°_{out}$) temperatures were measured. Fresh sodalime and charcoal were used. After baseline analysis, sevoflurane concentration was set at 2.1% end-tidal for 120 min. At baseline and at regular intervals thereafter, P_{ETCO_2}, end-tidal sevoflurane, $T°_{in}$, and $T°_{out}$ were measured. For inspiratory and expiratory compound A determination, samples of 2-ml gas were taken. These data were compared with those of a classical valve–containing closed-circuit machine. Ten runs were performed in each set-up.**

Results: **Inspired compound A concentrations increased from undetectable to peak at 6.0 (SD 1.3) and 14.3 (SD 2.5) ppm ($P < 0.05$), and maximal temperature in the upper outflow part of the absorbent canister was 24.3°C (SD 3.6) and 39.8°C (SD 1.2) ($P < 0.05$) in the PhysioFlex and valve circuit machines, respectively. Differences between the two machines in compound A concentrations and absorbent canister temperature at the inflow and outflow regions were significantly different ($P < 0.05$) at all times after 5 min.**

Conclusion: **Compound A concentrations in the high-flow (70 l/min), closed-circuit PhysioFlex machine were significantly lower than in conventional, valve-based machines during closed-circuit conditions. Lower absorbent temperatures, resulting from the high flow, appear to account for the lower compound A formation. (Key words: Anesthetic breakdown; carbon dioxide absorbent.)**

FROM the earliest use of sevoflurane, it was shown that this anesthetic agent can be degraded to several breakdown products, designated compounds A, B, C, D, and E, in an interaction with carbon dioxide absorbents. The fresh-gas flow rate during sevoflurane administration is a very important factor. From clinical data, it is generally concluded that the lower the fresh gas flow, the more compound A is formed.[1,2] Only one report (on five patients) has been published on compound A formation when using true quantitative closed-circuit anesthesia, and there is another report on eight patients, whereby such an apparatus was compared with a classical low flow system.[4] Closed-circuit conditions have been defined by Baum[5] in either nonquantitative anesthesia, whereby constancy of gas volume but not necessarily of anesthetic gas composition is obtained in the breathing circuit, and in quantitative anesthesia, whereby both of these factors are constant during the entire anesthetic period. The latter is only possible if both aspects are controlled electronically by closed-loop feedback.[6] In Europe, an anesthetic apparatus with computer-controlled liquid injection and automatic volume and concentration control has been available in routine clinical practice for 10 yr (PhysioFlex; Dräger, Lübeck, Germany). The aim of the present study was to assess the formation of compound A with this modern device during standardized laboratory conditions and to compare it with a conventional valve-containing closed-circuit set-up.

Methods

The Closed-circuit Anesthesia Apparatus

The PhysioFlex apparatus is capable of providing quantitative, self-regulating, target-controlled inhalational anesthesia, with a totally closed circuit of 3.5 l. The fresh gas flow to the circuit is intermittent, automatically regulated by continuous monitoring of the volume and composition of the gas mixture in the breathing circuit. The system is basically a valveless circuit in which the breathing gases are circulated at a flow rate of 70 l/min by an incorporated fan.[7] Four-membrane chambers, used for ventilation monitoring and volume generation, are built into the breathing system for the purpose of controlled ventilation. The displacement of the membranes generates and measures the tidal volume. The administration of the inhalational anesthetic is based on the injection of liquid anesthetic from a syringe directly into the breathing system. The amount of liquid anesthetic injected is immediately evaporated by the high constant gas flow in the breathing circuit.

The inspiratory oxygen concentration is measured continuously with a paramagnetic oxygen analyzer, whereas the concentrations of nitrous oxide, carbon dioxide, and volatile anesthetics are measured with a

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built-in infrared spectrometer. All measured values are continuously fed in into the 16-bit computer of the PhysioFlex, which controls ventilation, the injection system for administering sevoflurane, and the volume and composition of the gas mixture. According to the set parameters, small amounts of oxygen and nitrous oxide (or air) are given automatically; excess gases are evacuated if required.

For the administration of sevoflurane, a closed-loop feedback system is applied. The anesthetist can select a target end-tidal concentration of sevoflurane. According to the concentration measured by the gas analyzer, the stepping motor of the syringe pump is controlled *via* a proportional integrating and differentiating algorithm to reach and maintain the targeted end-tidal sevoflurane concentration. Hereby, an initial overshoot in the inspired concentration is observed. If it is necessary to lower the sevoflurane concentration, the circuit is exposed to a special canister, which is filled with activated charcoal, for removal of sevoflurane.

The second closed-circuit system analyzed is a classical valve circuit. To obtain the same internal system volume and compressible volume, we modified the original PhysioFlex apparatus slightly. The built-in fan was switched off (in normal practice this is not possible), and, in the breathing circuit, two standard unidirectional valves (Dräger) were incorporated. As the normally built-in computer controlling anesthetic injection is then nonfunctional, liquid sevoflurane was, in this second set-up, given by Graseby 3500 syringe-pump (Graseby, Watford, United Kingdom) injection in a small copper reservoir placed in the breathing circuit, according to the measured vapor concentrations (see below).

Experimental Design

To simulate clinical conditions, an artificial "living" test lung (Dräger) was used, simulating human oxygen consumption and carbon dioxide production, into which ≈ 160 ml/min carbon dioxide was introduced, aiming for an end-tidal carbon dioxide partial pressure (P_{ETCO_2}) of ≈ 40 mmHg. A continuous flow of ≈ 200 ml/min (simulating oxygen consumption) was sampled to a stand-alone Ultima analyzer (Datex, Helsinki, Finland) for uniform measurement and recording of all gas concentrations in both set-ups. Only oxygen was used in the breathing system. The ventilation rate was set at 10 breaths/min and the tidal volume at 490 ml. Temperatures were measured in the sodalime canister, which has a capacity of 800 ml, by thermistors (Arbo, Yellow Springs, OH), one situated in the lower inflow part ($T°_{in}$) and one in the upper outflow part ($T°_{out}$). Fresh sodalime (Sodasorb Grace, Epernon, France) containing, according to the manufacturer, NaOH 2.5%, KOH 1.5%, and $Ca(OH)_2$ 95%, was used for each run. The temperature at the Y-piece ($T°_{Y}$) was also measured with a thermistor.

After checking the airtightness of the PhysioFlex apparatus (this is part of the installation procedure), the anesthetic apparatus was connected to the artificial lung. In both circuits studied, the automatic constant-volume program was functional, whereby the "consumed oxygen" is replaced by the automatic injection of small quantities of oxygen (= fresh gas flow), which is shown digitally as "oxygen consumption." After initial adaptation, this value stabilized in both set-ups at approximately 200 ml/min, which was the amount taken out of the test lung.

Ten randomized independent runs were performed with both set-ups. After baseline analysis of all the data, sevoflurane was targeted at 2.1% end-tidal for 120 min; thereafter, sevoflurane administration was stopped. At baseline and at 5, 15, 30, 45, 60, 75, 90, 105, and 120 min after the start of sevoflurane and 5 and 10 min after its cessation, P_{ETCO_2}, end-tidal sevoflurane ($Sevo_{ET}$), $T°_{in}$, and $T°_{out}$ were recorded. In addition, 2-ml gas samples for inspiratory compound A (compound A_{insp}) and expiratory compound A (compound A_{exp}) analysis were taken in airtight syringes at the inspiratory and expiratory limb. The samples were always taken in duplicate. The syringes were attached to the anesthetic circuit by three-way valves and Luer-lock connections. The gas samples were then immediately transferred to sealed glass headspace vials and briefly stored at room temperature.

Compound A was assayed by capillary gas chromatography combined with mass spectrometric detection (HP 6890-5973 MSD; Hewlett-Packard, Palo Alto, CA). Injection was fully automated by a technique based on headspace sampling (1 ml). To place enough analyte mass onto the capillary column, cryofocusing on Tenax sorbent (Alltech, Deerfield, IL) (liquid nitrogen, −80°C) placed in the injector liner was applied. The use of a thick-film capillary column (CP-select 624, a 6 % cyanopropylphenyl-dimethylsilicone stationary phase; Chrompack, Middelburg, The Netherlands) allowed adequate retention and excellent isothermal separation (38°C). Helium was used as carrier gas at a flow rate of 1 ml/min. The mass spectrometric detector was operated in the full-scan mode. Transfer line and source temperatures were 100°C and 170°C, respectively. The mass spectrum (electron ionization mode) of compound A is characterized by prominent peaks at m/z 69, 128, 161, and 180, the latter representing the molecular ion (M^+). The ion at m/z 128 was selected as target ion for quantitative purposes. Before each analysis, a standard curve consisting of eight points was prepared and injected. Standards of compound A in the gas phase were prepared, departing from liquid volumetric dilutions of stock solutions of compound A and sevoflurane in ethyl acetate. 1-Iodo-2,2,2-trifluoroethane was chosen as an internal standard. Good linearity over a 0.5–75 ppm (vol/vol) range was obtained (average correlation coefficient, 0.996; n = 10). Within-day (n = 6) and total (n = 10) reproducibility were tested at three different concentrations levels (0.5, 10, and 75 ppm). The coefficients of variation ranged from 4.1% to 10.0 %. The limit of detection, using the signal-

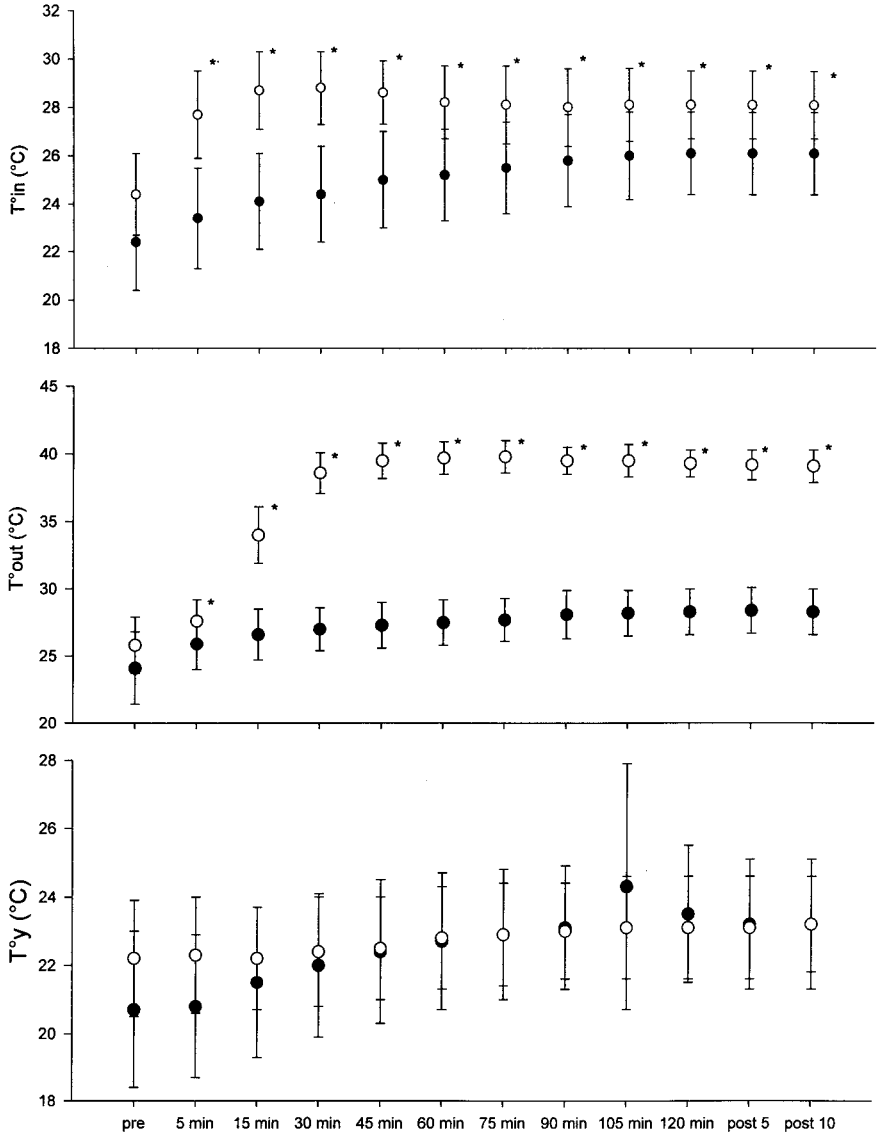

Fig. 1. Mean ± SD temperatures measured in the sodalime canister at the different examination times in both circuits (closed circles = PhysioFlex apparatus; open circles = valve circuit), decribed as $T°_{in}$ for the probe situated in the lower inflow part and as $T°_{out}$ for the probe situated in the upper outflow part. The temperature at the Y-piece ($T°_{Y}$) was also measured with a thermistor. *Intergroup $P < 0.05$ significance for the specific time assessment.

to-noise three criterion, was 0.1 ppm, while the limit of quantification was set at 0.3 ppm, signal-to-noise = 10, and the lowest point of the calibration curve to be measured with acceptable reproducibility (< 15%).

The data were analyzed using repeated-measures analysis of variance statistics. If statistical significance was found, a *post hoc* test (Tukey) was performed. For both groups, the correlation between compound A and temperature was analyzed. A Spearman's coefficient of rank correlation was calculated. For all tests, significance was set at $P < 0.05$.

Results

Mean P_{ETCO_2} was between 40 and 41 mmHg at the different times of examination in both circuits (differences not significant). The measured concentrations (mean ± SD) after targeting $Sevo_{ET}$ at 2.1% were around target (2.2 ± 0.2% and 2.1 ± 0.2% for the Physioflex and valve circuit machine, respectively) and not statistically different between groups; the differences between the two set-ups at the various times through 120 min were, from a practical viewpoint, not different. After stopping sevoflurane, the concentrations decreased sharply ($P < 0.01$) in the PhysioFlex circuit but not in the valve circuit (intergroup difference significant).

The canister temperatures ($T°_{in}$ and $T°_{out}$) are shown in figure 1. $T°_{out}$ was always higher than $T°_{in}$ in both circuits, but higher in the valve circuit than in the PhysioFlex circuit (intergroup difference $P < 0.05$ for each time point). $T°_{out}$ increased from 24.1 ± 2.7°C to 27.7 ± 1.6°C at 75 min in the PhysioFlex circuit and from 25.8 ± 2.1°C to 39.8 ± 1.2°C at 75 min in the valve circuit. The $T°_{Y}$ values are also shown in figure 1; no statistical difference was found at the various times between the two circuits.

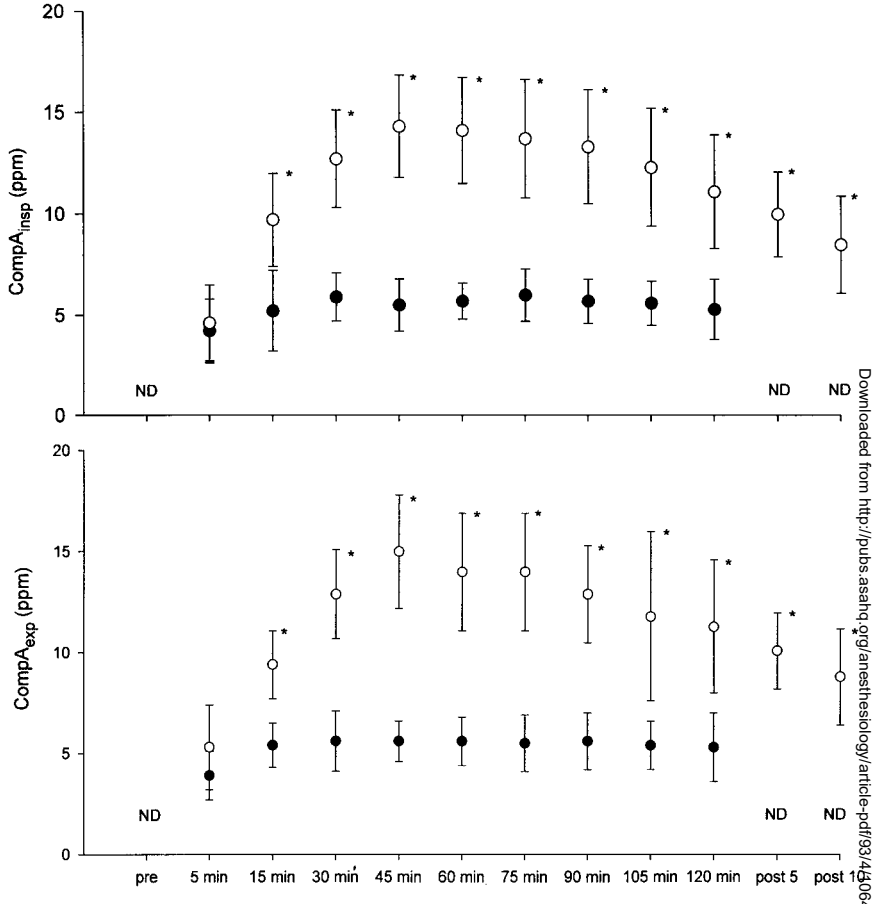

Fig. 2. Mean ± SD compound $A_{inspiratoir}$ ($_{(Comp\ A_{insp})}$) and compound $A_{expiratoir}$ (Comp A_{exp}) in both circuits (closed circles = PhysioFlex apparatus; open circles = valve circuit) at the different examination times. ND = nondetectable. *Intergroup $P < 0.05$ significance for the specific time assessment.

The results for compound A_{insp} and compound A_{exp} are shown in figure 2. Before sevoflurane, administration compound A was not detectable. Its concentration thereafter was always higher in the valve circuit than in the PhysioFlex circuit, and, except at 5 min, the differences between both circuits were significant at each time point (fig. 2). Compound A_{insp} increased from 4.2 ± 1.6 ppm to 6.0 ± 1.3 ppm at 75 min in the PhysioFlex circuit and from 4.6 ± 1.9 ppm to 14.3 ± 2.5 ppm at 45 min in the valve circuit. A scatter diagram of all compound A_{insp} and corresponding $T°_{out}$ values in both setups is shown in figure 3. A better correlation between both items was found in the valve circuit (r = 0.682) compared with the PhysioFlex circuit (r = 0.295).

Discussion

The compound A_{insp} and compound A_{exp}, as well as the canister $T°_{out}$ and $T°_{in}$, in the PhysioFlex circuit were similar to those found in a preliminary study[8] performed in our department, proving the repeatability of our experimental set-up.

In the present study, the concentrations of compound A within the valve circuit were considerably higher, at similar $Sevo_{ET}$ concentrations, than in the PhysioFlex circuit. The compound A concentrations in the PhysioFlex circuit are lower than reported by Bito and Ikeda[9] for closed-circuit anesthesia at similar $Sevo_{ET}$ concentrations, but come close to the data in a recent clinical study using the PhysioFlex apparatus but with other carbon dioxide absorbents.[3] The concentrations are almost identical to those reported by Bito *et al.*[4] when using the PhysioFlex machine. The compound A concentrations are even lower than those found by Ruzicka *et al.*[10] in an almost closed *in vitro* circuit with sevoflurane 1.5%, in which the sodalime was chilled to 26°C, whereas in their nonchilled sodalime group, compound A concentrations, and particularly canister temperatures, were higher than those found in our valve circuit. The sodalime temperatures and compound A concentrations in our valve containing closed circuit were somewhat less than those reported in several clinical low-flow or closed-circuit studies.[2,11,12] In our study, the compound A concentrations decreased after 75 min in both circuits.

The canister $T°_{out} - T°_{in}$ differences were low (≈ 2°C) in the PhysioFlex circuit, but pronounced (5–11°C) in the valve circuit. This small difference in the PhysioFlex apparatus is induced by the continuous flow of 70 l/min produced by the built-in fan, as by switching it off (valve circuit), not only did both $T°_{in}$ and $T°_{out}$ increase, but so did the difference between them. The continuous flow seems to shorten the contact time between the breathing gases and the sodalime, inducing heat dissipation

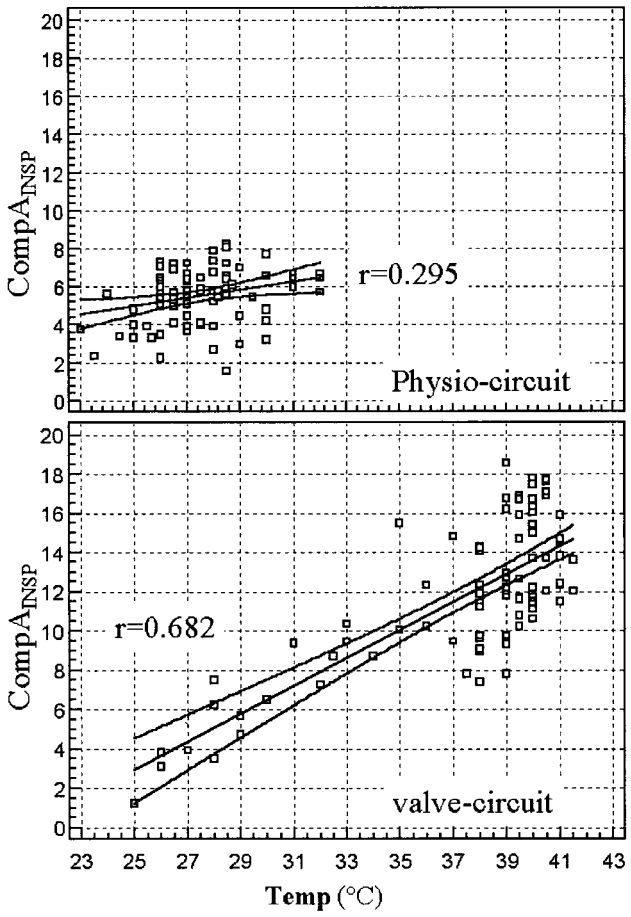

Fig 3. Scatter diagram of all measured temparatures at the upper outflow part of the sodalime canister ($T°_{out}$) and the inspiratory compound A (compound A_{insp}) concentrations in the PhysioFlex circuit (*upper*) and in the valve circuit (*lower*). The regression line and the 95% confidence lines are drawn for both circuits, and the correlation coefficients are mentioned.

further in the breathing system, a favorable effect on sodalime temperature. The temperature at the Y-piece (22–23°C; fig. 1) was, however, identical in both circuits and clinically acceptable.

Differences between compound A_{insp} and compound A_{exp} concentrations were almost nonexistent. This is hardly surprising, as, in contrast to the human body, the rubber artificial lung will barely take up any chemical substance. However, a small amount of compound A was evacuated with the continuing flow to the Ultima analyzer.

After cessation of sevoflurane administration, the sevoflurane concentration decreased sharply ($P < 0.01$) in the PhysioFlex circuit because of the opening of a special activated charcoal canister, built into the apparatus to decrease temporarily the anesthetic concentration or to get rid of the substance completely if such a command is given. The charcoal not only effectively adsorbs sevoflurane but also compound A, as it becomes undetectable after 5 and 10 min. In the valve circuit, after stopping sevoflurane administration, there was only a small decrease of $Sevo_{ET}$ and of compound A_{insp} and compound A_{exp} concentrations, as here no electrical impulse is given for opening the charcoal absorber. We also deliberately ignored the intermittently (≈ every 30 min) appearing message on the PhysioFlex screen to "flush the closed system," to get rid of some unwanted, accumulated foreign gases, which seemingly would also decrease compound A concentrations in this circuit.

In the valve circuit without the continuous flow of 70 l/min, higher compound A concentrations are formed and higher sodalime temperatures are found (fig. 3). As previous reports show a correlation between sodalime temperature and compound A formation,[12,13] the reason for the reduced formation of compound A is the lower sodalime temperature.

In conclusion, compound A concentrations in the high-flow (70 l/min), closed-circuit Physioflex machine were significantly lower than in conventional, valve-based machines during low-flow and closed-circuit conditions. Lower absorbent temperatures, resulting from the high flow, appear to account for the lower compound A formation. This gives this PhysioFlex computer-controlled system particular advantages for administering sevoflurane in closed-circuit anesthesia, without undue concern about the generation of compound A.

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