J Anesth (2010) 24:587–593
DOI 10.1007/s00540-010-0965-7

CLINICAL REPORT

Differential effects of hyperventilation on cerebral blood flow velocity after tourniquet deflation during sevoflurane, isoflurane, or propofol anesthesia

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Received: 16 December 2009 / Accepted: 24 April 2010 / Published online: 1 June 2010

Abstract The purpose of this study was to compare the degree of increase in middle cerebral artery (MCA) blood flow velocity after tourniquet deflation when modulating hyperventilation during orthopedic surgery under sevoflurane, isoflurane, or propofol anesthesia. Twenty-four patients undergoing elective orthopedic surgery were randomly divided into sevoflurane, isoflurane, and propofol groups. Anesthesia was maintained with sevoflurane, isoflurane, or propofol administration with 33% oxygen and 67% nitrous oxide at anesthetic drug concentrations adequate to maintain bispectral values between 45 and 50. A 2.0-MHz transcranial Doppler probe was attached to the patient's head at the temporal window, and mean blood flow velocity in the MCA (V_{mca}) was continuously measured. The extremity was exsanguinated with an Esmarch bandage, and the pneumatic tourniquet was inflated to a pressure of 450 mmHg. Arterial blood pressure, heart rate, V_{mca} and arterial blood gases were measured every minute for 10 min after release of the tourniquet in all three groups. Immediately after tourniquet release, the patients' respiratory rates were increased to tightly maintain end-tidal carbon dioxide ($PetCO_2$) at 35 mmHg. No change in partial pressure of carbon dioxide in arterial blood ($PaCO_2$) was observed pre- and posttourniquet deflation in any of the three groups. Increase in V_{mca} in the isoflurane group was greater than that in the other two groups after tourniquet deflation. In addition, during the study period, no difference in V_{mca} after tourniquet deflation was observed between the propofol and sevoflurane groups. Hyperventilation could prevent an increase in V_{mca} in the propofol and sevoflurane groups after tourniquet deflation. However, hyperventilation could not prevent an increase in V_{mca} in the isoflurane group.

Keywords Volatile anesthetics · Propofol · Cerebral blood flow velocity · Hyperventilation

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Introduction

Pneumatic tourniquets are used on the extremities to obtain a bloodless surgical field during orthopedic surgery [1]. However, although it is a beneficial tool, ischemic metabolites released after tourniquet deflation provoke several physiological alterations [1–4]. Decreases in arterial pH or increases in partial pressure of carbon dioxide in arterial blood ($PaCO_2$) and lactate are known to occur immediately after tourniquet deflation [2–4]. $PaCO_2$ plays a central role in the regulation of cerebral vasomotor tone [5]. Elevation in $PaCO_2$ results in dilation of cerebral arteries and, consequently, increased cerebral blood flow (CBF). The rapid elevation in $PaCO_2$ reported after tourniquet deflation [1–4] would thus be expected to result in a corresponding increase in CBF. There have been several reports examining the alterations in CBF or CBF velocity after tourniquet deflation [2, 3]. The study by Hirst et al. [3] and our previous report [2] showed that a transient increase in CBF does occur after tourniquet deflation. In addition, we previously showed that hyperventilation could prevent this increase in middle cerebral artery (MCA) blood-flow

velocity induced by elevated $PaCO_2$ after tourniquet deflation [2].

The use of anesthetic agents such as isoflurane, sevoflurane, or propofol could produce altered vasodilatory or vasoconstrictive responses in cerebral arteries in response to changes in arterial CO_2 [6–8]. In previous studies, we found that different anesthetic agents have differential effects on the degree of increase in MCA flow velocity in response to increases in $PaCO_2$ [8]. Strebel et al. [9] also found differential effects of anesthetic agents on cerebral circulation and autoregulation in humans. We hypothesized that hyperventilation, used to control the degree of increase in MCA blood flow after tourniquet deflation, would have a different time course of effects with different anesthetic agents. The transient increase in CBF after tourniquet deflation may have a detrimental effect in patients with cerebral complications, such as head injury [10, 11]. Thus, it is clinically important for anesthesiologists to know whether selection of particular anesthetic agents would be useful for avoiding the transient increase in CBF after tourniquet deflation. The purpose of this study was thus to compare the increase in MCA blood flow velocity when modulating $PaCO_2$ with hyperventilation after tourniquet deflation during orthopedic surgery under sevoflurane, isoflurane, pr propofol anesthesia.

Case report

After obtaining approval of the ethics committee of our institution, written informed consent was obtained from all patients. Twenty-four patients undergoing elective orthopedic surgery requiring the use of a tourniquet on the lower extremity were studied. None of the patients had pulmonary, renal (plasma creatinine concentration >2.0 mg/dl), or hepatic disease (glutamine oxaloacetate transaminase or glutamine pyruvate transaminase >50 U/dl). The absence of neurological diseases and cerebrovascular disorders was confirmed by preoperative cerebral computed tomography (CT). None of the patients in this study had carotid artery stenosis, defined as luminal narrowing of >50%, as assessed by preoperative ultrasonography and magnetic resonance imaging (MRI). The 24 patients were randomly divided into three groups (sevoflurane, isoflurane, and propofol) determined by a random number table.

A three-lead electrocardiography monitor was attached to all patients (Hewlett Packard, Andover, MA, USA). Anesthesia was induced with 2 mg/kg propofol, 5 μg/kg fentanyl, or 0.1 mg/kg vecuronium, followed by endotracheal intubation. Muscle relaxation was achieved by intermittent administration of vecuronium. The left radial artery was cannulated with a 22-gauge indwelling catheter to monitor arterial blood pressure and to measure arterial blood gas and plasma lactate levels. All patients were mechanically ventilated, with continuous monitoring of end-tidal carbon dioxide ($PetCO_2$) (Hewlett Packard, Andover, MA, USA). Anesthesia was maintained with sevoflurane, isoflurane, or propofol with 33% oxygen and 67% nitrous oxide. Bispectral index (BIS) monitoring (A-2000, ASPECT Medical Systems, Natick, MA, USA) was used to maintain equipotent doses of sevoflurane, isoflurane, or propofol in each group. Target BIS levels were from 45 to 50, the doses of anesthetic agents being adjusted to maintain anesthesia at these levels during the study period. The sevoflurane and isoflurane concentrations required to maintain target BIS values were very close to 1.0 minimum alveolar anesthetic values (MAC). A 2.0-MHz transcranial Doppler (TCD) probe (TC2-64; EME Co., Ltd., Uberlingen, Germany) was attached to the patient's head at the right temporal window, and mean blood flow velocity in the middle cerebral artery (V_{mca}), as an index of CBF, was measured continuously. Signal quality was determined by the characteristic high-pitched sound and the waveform of the sonogram display. After the signals were identified at a depth of 45–60 mm, the probe was fixed using a probe holder so as not to change the insonation angle.

Study protocol

The extremity being operated on was exsanguinated with an Esmarch bandage and the pneumatic tourniquet inflated to a pressure of 450 mmHg. Lactated Ringer's solution was infused throughout surgery at the rate of 5 ml/kg/h. After anesthetic induction, ventilation was controlled with a tidal volume of 8–10 ml/kg body weight and a respiratory rate of 8–12 breaths per minute to maintain the $PetCO_2$ at 35 mmHg. In addition, 2 or 3 min before release of the tourniquet, ventilatory rate or tidal volume was adjusted to tightly maintain the $PetCO_2$ at 35 mmHg. After tourniquet release, $PetCO_2$ was tightly maintained at 35 mmHg by increasing the respiratory rate.

Arterial blood pressure, heart rate, V_{mca}, arterial blood gases and plasma lactate levels were measured every minute for 10 min after tourniquet release in all patients, using a Stat Profile Ultima^R (NOVA Biomedical Co., Boston, MA, USA). All data are expressed as mean ± standard deviation (SD). Following the confirmation of equal variance among groups by the Bartlett test, the χ^2 test or one-way factorial or repeated measures analysis of variance was performed with multiple comparisons. When the F value was significant, the Bonferroni method was used to make multiple comparisons. Statistical significance was set at $P < 0.05$. All calculations were performed on a Macintosh computer with SPSS (SPSS, Chicago, IL, USA)

Table 1 Demographic data of the three groups

	Sevoflurane	Isoflurane	Propofol	*P* value
Number	8	8	8	
Age (years)	57 ± 11	61 ± 8	60 ± 10	0.65
Weight (kg)	56 ± 7	56 ± 7	61 ± 5	0.24
Height (cm)	156 ± 4	157 ± 5	160 ± 6	0.30
Anesthetic time (min)	225 ± 27	203 ± 31	224 ± 37	0.32
Operation time (min)	147 ± 21	131 ± 18	143 ± 21	0.30
Tourniquet time (min)	93 ± 10	90 ± 8	95 ± 8	0.54
End-tidal agent concentration (%)	1.50 ± 0.05	1.06 ± 0.04		
BIS predeflation	44 ± 2	45 ± 2	44 ± 2	0.89

Data are expressed as mean ± standard deviation

BIS bispectral index

and Stat View 5.0 software packages (Abacus Concepts, Berkeley, CA, USA). Table 1 shows the demographic data of the three groups. There were no significant differences among groups. All patients had easily detectable MCA flow velocities. Target BIS levels of 45–50 during the study period were maintained with mean propofol infusion rates of 7.7 ± 0.6 mg/kg per min (7.0–8.8), mean averages of end-tidal sevoflurane concentrations of 1.50 ± 0.05%, or end-tidal isoflurane concentrations of 1.06 ± 0.04% during the study period at 10 min. There were no significant differences in BIS values immediately predeflation (Table 1).

Table 2 shows the time course of changes in physiological variables in the three groups. Mean arterial pressure (MAP) in all three groups decreased for 3 min after tourniquet deflation. Heart rates (HR) in all three groups increased after tourniquet deflation, the increase lasting for 1–3 min. No change in $PaCO_2$ was observed pre- and posttourniquet deflation in the three groups. Plasma pH levels in the three groups decreased after tourniquet deflation, the decrease lasting for 7 min. Plasma lactate levels in the three groups increased for 10 min after tourniquet deflation.

Table 3 shows the time course of changes in V_{mca} and the significant differences in V_{mca} alterations between the groups. Predeflation, V_{mca} in the isoflurane group was greater than that in the other two groups. The increase in V_{mca} in the isoflurane group was also greater than that in the other two groups after tourniquet deflation. In addition, no difference in V_{mca} after tourniquet deflation between the propofol and sevoflurane groups was observed during the study period.

Discussion

The study shows that hyperventilation, sufficient to maintain $PaCO_2$ at pretourniquet deflation levels, could prevent an increase in V_{mca} in the propofol and sevoflurane groups after tourniquet deflation. However, hyperventilation could not prevent an increase in V_{mca} in the isoflurane group, which lasted for 4 min after tourniquet deflation. There have been some reports examining changes in CBF or MCA velocity after tourniquet deflation. Hirst et al. [3] examined the effects of intraoperative release of a thigh tourniquet on MCA blood flow using TCD ultrasonography and found that MCA flow velocity increased significantly from 52 ± 6 to 82 ± 24 cm/s (an increase of 58 ± 13%) within 4 ± 1 min after tourniquet release and remained elevated for 7 min. Fujii et al. [12] examined the effects on the MCA of tourniquet release on the upper and lower extremities and found that the increase in MCA blood flow velocity was greater in patients requiring lower-extremity tourniquets than in those with upper-extremity tourniquets. These two studies demonstrated that increased MCA flow velocity was mainly attributable to an increase in $PaCO_2$. In an interesting study, Akata et al. [13] showed that the increase in $PetCO_2$ in spontaneously breathing patients was smaller than that in ventilation-controlled patients because of the compensatory increase in respiratory rate in spontaneously breathing patients. Tsuchiya et al. [4] suggested the possible beneficial effects of hyperventilation immediately after tourniquet deflation to prevent this increase in V_{mca}. Indeed, we previously showed that hyperventilation immediately after tourniquet deflation could prevent an increase in V_{mca} under propofol anesthesia [2].

Anesthetic agents such as sevoflurane, isoflurane, and propofol could modulate cerebral circulation [9]. Recently, we found that different anesthetic agents exert a differential time course of changes in V_{mca} after tourniquet deflation [14]. This strongly suggests that V_{mca} may differ with the patient under different anesthetic agents when hyperventilation is used after tourniquet deflation. Our hypothesis was confirmed by our finding showing a differential time course of changes in V_{mca} with hyperventilation under anesthesia with different anesthetic agents. There are several possible mechanisms for this effect.

Table 2 Time course of changes in physiological variables in the three groups

Group	Predeflation	Time from tourniquet deflation (min)									
		1	2	3	4	5	6	7	8	9	10
MAP (mmHg)											
Propofol	101 ± 11	88 ± 11*	86 ± 7*	89 ± 7*	92 ± 12	93 ± 9	99 ± 11	97 ± 11	104 ± 12	104 ± 12	105 ± 13
Sevoflurane	104 ± 6	89 ± 12*	90 ± 9*	88 ± 8*	93 ± 10	95 ± 8	97 ± 5	101 ± 9	103 ± 11	101 ± 10	100 ± 9
Isoflurane	104 ± 8	86 ± 9*	88 ± 7*	89 ± 7*	92 ± 9	93 ± 6	97 ± 5	94 ± 9	100 ± 12	103 ± 8	104 ± 11
HR (beats/min)											
Propofol	72 ± 5	89 ± 7*	84 ± 9	77 ± 6	74 ± 5	78 ± 5	75 ± 5	75 ± 6	77 ± 5	74 ± 6	77 ± 5
Sevoflurane	76 ± 6	91 ± 7*	88 ± 6*	79 ± 6	74 ± 6	78 ± 5	77 ± 6	76 ± 6	79 ± 7	77 ± 8	78 ± 4
Isoflurane	75 ± 5	90 ± 7*	87 ± 6*	81 ± 6*	76 ± 5	77 ± 5	75 ± 5	76 ± 5	74 ± 6	76 ± 4	75 ± 7
pH											
Propofol	7.449 ± 0.03	7.409 ± 0.03*	7.409 ± 0.03*	7.383 ± 0.03*	7.399 ± 0.04*	7.401 ± 0.03*	7.405 ± 0.02*	7.411 ± 0.05*	7.425 ± 0.04	7.444 ± 0.04	7.434 ± 0.04
Sevoflurane	7.445 ± 0.05	7.399 ± 0.04*	7.386 ± 0.04*	7.388 ± 0.05*	7.400 ± 0.05*	7.399 ± 0.05*	7.403 ± 0.04*	7.415 ± 0.04*	7.429 ± 0.05	7.440 ± 0.05	7.440 ± 0.05
Isoflurane	7.447 ± 0.05	7.402 ± 0.04*	7.390 ± 0.05*	7.390 ± 0.05*	7.401 ± 0.05*	7.400 ± 0.05*	7.406 ± 0.04*	7.412 ± 0.04*	7.430 ± 0.04	7.448 ± 0.04	7.439 ± 0.04
$PaCO_2$ (mmHg)											
Propofol	35 ± 1	36 ± 2	35 ± 2	35 ± 1	36 ± 1	36 ± 2	37 ± 2	35 ± 2	35 ± 1	35 ± 1	35 ± 1
Sevoflurane	35 ± 1	36 ± 2	36 ± 2	36 ± 2	36 ± 2	36 ± 2	34 ± 2	37 ± 2	36 ± 1	34 ± 1	35 ± 1
Isoflurane	36 ± 1	35 ± 2	34 ± 2	35 ± 1	35 ± 2	35 ± 2	36 ± 2	36 ± 1	37 ± 2	35 ± 1	35 ± 1
PaO_2 (mmHg)											
Propofol	181 ± 19	177 ± 20	171 ± 18	169 ± 16	171 ± 19	170 ± 19	164 ± 26	170 ± 17	168 ± 14	166 ± 16	167 ± 17
Sevoflurane	169 ± 17	170 ± 21	174 ± 16	169 ± 18	170 ± 18	170 ± 18	166 ± 21	168 ± 18	169 ± 19	169 ± 20	165 ± 18
Isoflurane	172 ± 19	170 ± 16	170 ± 19	168 ± 21	170 ± 18	172 ± 15	170 ± 18	169 ± 14	166 ± 20	164 ± 20	168 ± 15
Lactate (mmol/L)											
Propofol	0.9 ± 0.3	2.1 ± 0.4*	2.5 ± 0.4*	2.5 ± 0.3*	2.4 ± 0.4*	2.1 ± 0.3*	2.2 ± 0.3*	2.0 ± 0.3*	1.9 ± 0.3*	2.0 ± 0.4*	2.0 ± 0.3*
Sevoflurane	1.0 ± 0.2	2.2 ± 0.4*	2.4 ± 0.5*	2.4 ± 0.4*	2.3 ± 0.4*	2.2 ± 0.4*	2.1 ± 0.3*	2.1 ± 0.4*	2.0 ± 0.3*	2.0 ± 0.4*	2.1 ± 0.4*
Isoflurane	1.1 ± 0.2	2.3 ± 0.4*	2.4 ± 0.3*	2.5 ± 0.4*	2.3 ± 0.4*	2.2 ± 0.3*	2.2 ± 0.3*	2.2 ± 0.4*	2.0 ± 0.4*	2.0 ± 0.3*	2.0 ± 0.4*

Data are expressed as mean ± standard deviation (SD)

MAP mean arterial pressure; *HR* heart rate, *$PaCO_2$* partial pressure of carbon dioxide in arterial blood, *PaO_2* partial pressure of oxygen in arterial blood

* $P < 0.05$ compared with predeflation period

Table 3 Time course of changes in mean blood flow velocity in the middle cerebral artery (V_{mca}) in the three groups

Group	Predeflation	Time from tourniquet deflation (min)									
		1	2	3	4	5	6	7	8	9	10
V_{mca} (cm/s)											
Propofol	39.1 ± 2.1	42.8 ± 1.7	44.6 ± 1.6	43.0 ± 3.2	44.3 ± 3.2	42.6 ± 2.2	41.1 ± 1.3	39.7 ± 1.2	38.3 ± 1.7	38.3 ± 1.8	38.5 ± 1.3
Sevoflurane	39.8 ± 0.9	43.8 ± 3.0	44.2 ± 4.8	44.5 ± 5.7	44.1 ± 5.4	43.5 ± 4.5	42.7 ± 4.4	43.2 ± 5.0	40.7 ± 2.8	40.3 ± 4.0	40.1 ± 3.4
Isoflurane	44.8 ± 3.6**	55.2 ± 3.5*·**	54.6 ± 3.3*·**	55.7 ± 4.8*·**	53.0 ± 2.9*·**	51.3 ± 3.0**	49.0 ± 3.1**	46.2 ± 2.5	44.8 ± 2.2	43.6 ± 2.5	44.0 ± 3.2
V_{mca} (%) (% of prerelease value)											
Propofol	100	107 ± 3	112 ± 3	109 ± 4	112 ± 4	107 ± 3	105 ± 4	100 ± 3	97 ± 3	97 ± 3	97 ± 3
Sevoflurane	100	110 ± 3	112 ± 4	112 ± 5	112 ± 4	110 ± 5	107 ± 3	110 ± 3	102 ± 3	102 ± 3	102 ± 4
Isoflurane	100	125 ± 4*·**	122 ± 4*·**	125 ± 5*·**	120 ± 3*·**	115 ± 4	111 ± 4	105 ± 4	100 ± 4	97 ± 4	100 ± 4

Data are expressed as mean ± standard deviation (SD)

* $P < 0.05$ compared with predeflation period

** $P < 0.05$ compared with other two groups at the same time point

Propofol has been reported to produce dose-dependent cerebral vasoconstriction. Eng et al. [15] demonstrated that V_{mca} in awake patients was 63 ± 5 cm/s at a $PaCO_2$ of 40 mmHg, whereas with an infusion of propofol at 150 μg/kg per min, V_{mca} decreased to 38 ± 3 cm/s at the same $PaCO_2$. In a study using TCD ultrasonography [8], we showed that propofol exerts a dose-dependent cerebral vasoconstrictive effect. In contrast, volatile anesthetics such as sevoflurane and isoflurane produce cerebral vasodilation [6, 16, 17]. Nishiyama et al. [6] showed that although both agents dilated the cerebral vasculature, the potency of this effect was greater with isoflurane than with sevoflurane at the same MAC. From the above-mentioned reports from other researchers regarding the effects on cerebral autoregulation [9, 16] and from our previous studies [8, 17], the observations of this study may be attributable to the difference in the strength of the cerebrovascular response to CO_2 under each anesthetic agent. Since cerebrovascular CO_2 reactivity is greater with isoflurane than with sevoflurane at the same MAC, and since propofol produces cerebral vasoconstriction, V_{mca} responses to changes in $PaCO_2$ after tourniquet deflation are greater with isoflurane than in the other two groups at the same $PaCO_2$ level. Since the cerebral artery in the propofol group was already under propofol-induced vasoconstriction at the predeflation point, further vasoactive changes in V_{mca} after tourniquet deflation could not occur compared with the other two groups.

McPherson et al. [18] examined CBF responsiveness to alterations in $PaCO_2$ during 1.4 and 2.8% isoflurane anesthesia in dogs and found that the degree of decrease in CBF with hyperventilation was different. Previously, we showed that different propofol dosages affected different cerebrovascular CO_2 reactivities in elderly patients [8], suggesting the possibility that different results would be found with the use of different concentrations of the same anesthetic. Another possibility of the differential change in V_{mca} by hyperventilation may be attributable to the differential rate of change in V_{mca}. Chong et al. [19] compared the rate of changes of V_{mca} when $PetCO_2$ was rapidly altered during halothane or isoflurane anesthesia and showed that the rate of change of CBF velocity was faster in the isoflurane than in the halothane group, especially in the initial few minutes. Even when the $PaCO_2$ was equal in this study, a slight time lag of several seconds in controlling the $PaCO_2$ may have occurred. This time lag may have impacted our findings, as would have the differential response rate of changes in V_{mca} in response to $PaCO_2$ with each anesthetic agent. In addition, since there was a difference in absolute V_{mca} between the three groups at the predeflation point, the degree of cerebrovascular response to $PaCO_2$ may also have been different due to different CO_2 reactivities. Finally, other factors, such as decrease in pH and increase

in lactate, may affect the results. Although equal degrees of changes in pH and lactate after tourniquet deflation were observed, we cannot rule out the possibility that the reactivities of cerebral vessels to pH and lactate may be different under different anesthetic agents.

This study demonstrated that hyperventilation immediately after tourniquet deflation could not prevent an increase in V_{mca} under isoflurane anesthesia. V_{mca} is an accepted index of CBF [5]. Even a transient increase in CBF after tourniquet release may have detrimental effects in patients with cerebral complications, such as head injury. Indeed, Conaty et al. [10] and Eldridge et al. [11] reported that the increase in CBF could induce serious elevation of intracranial pressure in patients with head injury after tourniquet deflation. The clinical implication of our study is that when hyperventilation is used to avoid a possible transient increase in CBF, anesthesiologists should be aware of the differential effects of different anesthetic agents on V_{mca} after tourniquet deflation. In clinical practice, a combination of nitrous oxide and volatile/intravenously administered anesthetics is commonly used. Hence, we examined V_{mca} alteration during anesthesia with propofol, sevoflurane, or isoflurane administered together with nitrous oxide. It is reported that this combination has a more potent cerebral vasodilatory effect than an equipotent dose of volatile anesthetic alone [20]. It is thus possible that the cerebral vasodilatory effect with a combination of propofol, sevoflurane, or isoflurane and nitrous oxide may reduce the ability of the cerebral vasculature to further dilate in response to CO_2. Hence, we cannot rule out the possibility that nitrous oxide may have different effects on cerebral circulation when used in combination with different anesthetics. Moreover, as some researchers reported that nitrous oxide might have harmful effects on the brain in patients with head injury, we need to further examine the effects of propofol, sevoflurane, or isoflurane on cerebral circulation without nitrous oxide. In addition, although induction anesthetics such as propofol or fentanyl may have had some effects on V_{mca}, after tourniquet deflation in our study, the measurement points were long enough after induction to ignore the effects of these agents on our results.

In conclusion, hyperventilation could prevent an increase in V_{mca} under propofol and sevoflurane anesthesia after tourniquet deflation. In contrast, hyperventilation could not prevent an increase in V_{mca} under isoflurane anesthesia. Thus, anesthetic agents modulate hyperventilation-induced V_{mca} changes after tourniquet deflation in patients undergoing orthopedic surgery.

Acknowledgments The authors thank Forte (Tokyo, Japan) for assistance with manuscript preparation in English. This study was supported in part by grants to Dr. Kadoi (No.21591998) from the Japanese Ministry of Education, Culture, Sports, Science and Technology.

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