

# A Randomized Crossover Comparison of the Effects of Propofol and Sevoflurane on Cerebral Hemodynamics during Carotid Endarterectomy

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**Background:** Intravenous and inhalational anesthetic agents have differing effects on cerebral hemodynamics: Sevoflurane causes some vasodilation, whereas propofol does not. The authors hypothesized that these differences affect internal carotid artery pressure (ICAP) and the apparent zero flow pressure (critical closing pressure) during carotid endarterectomy. Vasodilation is expected to increase blood flow, reduce ICAP, and reduce apparent zero flow pressure.

**Methods:** In a randomized crossover study, the gradient between systemic arterial pressure and ICAP during carotid clamping was measured while changing between sevoflurane and propofol in 32 patients. Middle cerebral artery blood velocity, recorded by transcranial Doppler, and ICAP waveforms were analyzed to determine the apparent zero flow pressure.

**Results:** ICAP increased when changing from sevoflurane to propofol, causing the mean gradient between arterial pressure and ICAP to decrease by 10 mmHg (95% confidence interval, 6–14 mmHg;  $P < 0.0001$ ). Changing from propofol to sevoflurane had the opposite effect: The pressure gradient increased by 5 mmHg (95% confidence interval, 2–7 mmHg;  $P = 0.002$ ). Ipsilateral middle cerebral artery blood velocity decreased when changing from sevoflurane to propofol. Cerebral steal was detected in one patient after changing from propofol to sevoflurane. The apparent zero flow pressure (mean  $\pm$  SD) was  $22 \pm 10$  mmHg with sevoflurane and  $30 \pm 14$  mmHg with propofol ( $P < 0.01$ ). There was incomplete drug crossover due to the limited duration of carotid clamping.

**Conclusions:** Compared with sevoflurane, ipsilateral ICAP and apparent zero flow pressure are both higher with propofol. Vasodilation associated with sevoflurane can cause cerebral steal.

GENERAL anesthesia is commonly administered to patients having carotid endarterectomy. Although it is known that general anesthetic agents differ in their effects on the cerebral vasculature, it is not known whether these differences affect cerebral hemodynamics during clamping of the carotid artery. Our aim in this study was to compare the effects of two commonly used

anesthetic agents, propofol and sevoflurane, on cerebral hemodynamics during carotid clamping.

Internal carotid artery pressure (ICAP) measurement during carotid clamping (often referred to as the “stump pressure”) is useful as a monitor of pressure within arteries supplying the brain on the side of clamping. It is known that arterial pressure at the origin of the middle cerebral artery (MCA) is equal to ICAP.<sup>1</sup> Therefore, if intracranial pressure remains constant, changes in ICAP indicate a change in perfusion pressure for the brain regions supplied by the branches of the circle of Willis on that side.

In recent years, there has been increased interest in the concept of critical closing pressure (CCP) and its application to the cerebral circulation. As arterial pressure decreases, blood flow through a vascular bed ceases before the pressure gradient across the vascular bed reaches zero. This phenomenon is thought to be due to a combination of forces tending to close arterioles, *i.e.*, extra mural pressure and vessel wall tone. Conventionally, the downstream pressure of the cerebral circulation is assumed to be the greater of intracranial pressure or central venous pressure. However, according to the CCP model, blood pressure at the distal end of arterioles cannot be lower than the CCP, and therefore, CCP is the effective downstream pressure.<sup>2</sup> According to this model, it is the gradient between arterial pressure and CCP that determines flow, rather than the gradient between arterial pressure and intracranial pressure. Studies of instantaneous radial arterial pressure and MCA blood velocity (MCABV) within individual cardiac cycles have demonstrated a linear relation between pressure and velocity, and extrapolation of this linear relation predicts that flow would cease at a pressure above zero.<sup>3–5</sup> This apparent zero flow pressure (aZFP) has been proposed as an estimate of CCP.<sup>3</sup> The aZFP has not previously been investigated during carotid clamping.

During carotid clamping, ICAP is influenced by changes in cerebral vascular tone. For example, it has long been known that hypocapnia-induced cerebral vasoconstriction leads to an increase in ICAP, whereas hypercapnia leads to a decrease.<sup>6</sup> More recently, we have shown that autoregulatory vasodilation occurring immediately after carotid clamping is associated with a simultaneous decrease in ICAP.<sup>7</sup> Changes in arteriolar tone also affect the aZFP: Hypercapnia decreases and hypocapnia increases aZFP.<sup>4,8</sup> In animal models, aZFP is decreased by hypercapnia, hypoxia, and hypotension, all

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of which decrease arteriolar tone.<sup>9,10</sup> The inverse of the slope of the dynamic velocity–pressure relation may be taken as an index of cerebral vascular resistance. There is less published information regarding factors influencing the slope. Some experiments have found that increases or decreases in arterial carbon dioxide change the aZFP but not the velocity–pressure slope,<sup>9,11</sup> and this observation has been taken to imply that the reactivity of the cerebral circulation to carbon dioxide is dependent on changes in CCP and not changes in resistance.<sup>12</sup>

Volatile inhalational anesthetic agents, including sevoflurane, tend to cause cerebral vasodilation,<sup>13,14</sup> whereas the intravenous agent propofol does not.<sup>15,16</sup> In this study, we recorded ICAP and MCABV during carotid artery clamping while crossing over between propofol and sevoflurane in a randomized order. We hypothesized that, similar to the effect of hypercapnia, cerebral vasodilation with sevoflurane would lead to a lower ICAP. We also hypothesized that vasodilation with sevoflurane could be detected by an increased MCABV, a decreased aZFP, and/or an increased slope of the velocity–pressure relation.

## Materials and Methods

After approval by the local ethics review committee (Central Sydney Area Health Service, New South Wales, Australia), written informed consent was obtained from patients scheduled to undergo carotid endarterectomy. All patients underwent general anesthesia with tracheal intubation and mechanical ventilation.

### Monitoring

Routine monitoring included airway concentrations of carbon dioxide and sevoflurane. Systemic arterial blood pressure was monitored *via* a radial arterial catheter. A two-channel electroencephalogram was recorded *via* surface electrodes placed to monitor the cortical territory supplied by the MCA on each side. The Bispectral Index (BIS) was monitored using the A-2000 BIS<sup>®</sup> monitor (Aspect Medical Systems, Newton MA) *via* frontal electrodes placed according to the manufacturer's instructions. Peak MCABV was monitored by transcranial Doppler (Multidop-T; DWL, Sippligen, Germany). After identifying the MCA signal, the Doppler probes were held in constant position by attachment to a Lam-rack.<sup>17</sup>

Carotid stump pressure was measured at the time of clamping *via* a needle placed distal to the clamp. After removing the needle and performing the arteriotomy, the surgeon advanced a Fogarty balloon catheter into the internal carotid artery and inflated the balloon to prevent back-bleeding, thus obviating the need for a vascular clamp on the internal carotid artery. We used a balloon catheter incorporating a lumen opening at the catheter tip (distal to the balloon), and this lumen was connected

to a pressure transducer, thus enabling continuous monitoring of ICAP during the endarterectomy. The balloon catheter was removed just before completion of the arterial repair. Pressure transducers for monitoring radial artery pressure and ICAP were referenced to atmospheric pressure and placed at the height of the external auditory meatus.

### Experimental Procedures

We used a randomized crossover design to compare sevoflurane and propofol. Immediately before induction, patients were randomized to one of two groups by a randomization program on a handheld computer. The propofol–sevoflurane group (PS) had general anesthesia induced and maintained with a propofol infusion until the carotid artery was clamped, the arteriotomy was performed, and ICAP monitoring was established *via* the balloon catheter. At this time, the propofol infusion was stopped and sevoflurane introduced. The other group, sevoflurane–propofol (SP), had general anesthesia induced and maintained with sevoflurane until the carotid artery was clamped, the arteriotomy was performed, and ICAP monitoring was established *via* the balloon catheter, after which administration of sevoflurane was stopped and propofol was introduced. The doses of anesthetic agents were adjusted to aim for a BIS score between 40 and 55 throughout the study. To maintain the BIS score within the target range during the crossover between anesthetic agents, the second agent was introduced gradually as the effect of the initial agent declined.

In both groups, the trachea was intubated after paralysis with 50 mg rocuronium, and the lungs were ventilated with 100% oxygen (with or without sevoflurane). Ventilation was adjusted to achieve an end-tidal carbon dioxide concentration of 30–35 mmHg. Arterial carbon dioxide partial pressure was then measured, and ventilation was adjusted if necessary to aim for an arterial carbon dioxide partial pressure of 35–45 mmHg. During the period of drug crossover, ventilation was adjusted if required to maintain each patient's end-tidal carbon dioxide concentration constant within  $\pm 2$  mmHg. An intravenous infusion of remifentanyl ( $3\text{--}6 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ) was commenced with induction and maintained at a constant infusion rate throughout the study. Phenylephrine was infused as required to aim for a mean arterial pressure (MAP) of 90–100 mmHg and to aim for a constant MAP during the crossover of anesthetic agents.

Propofol was administered by a target-controlled infusion pump incorporating the Diprifusor (IVAC P6000 TCI; Alaris Medical Systems, Hampshire, United Kingdom) pharmacokinetic algorithm. The Diprifusor algorithm controls the infusion of propofol to attempt to achieve a specified target plasma propofol concentration. The pump displays an estimate of the plasma

propofol concentration and the effect site propofol concentration.

**Arterial Shunting.** According to the routine practice of the treating surgeon and anesthetist, a bypass shunt was placed if there was concern regarding the adequacy of cerebral perfusion (based on a low stump pressure, electroencephalographic changes, or both). In these patients, the study was abandoned.

**Data Collection and Analysis.** A 12-bit analog-to-digital recording system (Powerlab; ADInstruments, Sydney, Australia) was used to record the following parameters on a Macintosh personal computer at a sampling rate of at least 40 Hz: systemic arterial pressure, ICAP, outline of the MCABV waveform, and airway concentrations of sevoflurane and carbon dioxide. The BIS score and the estimated effect site concentration of propofol, as displayed by the target-controlled infusion pump, were recorded manually.

The primary variable of interest in this study was the change in the MAP-ICAP pressure gradient. Secondary variables of interest were the changes in MCABV and aZFP. From the recorded waveforms, the MAP, mean ICAP, and mean MCABV were determined at two times during the period of carotid clamping: (1) immediately before initiating crossover between the study drugs and (2) before removal of the internal carotid artery balloon catheter. At each of these times, the data were averaged over two or three complete respiratory cycles to control for respiratory swings in blood pressure and MCABV.

As suggested by Aaslid *et al.*,<sup>5</sup> we used the magnitudes of the fundamental (first harmonic) components of the ICAP and MCABV waveforms, calculated by Fourier analysis, to estimate aZFP. Distortions of pressure waveforms, occurring either within the arterial tree or within the measuring system, tend to affect the higher-frequency components of the signal more than the lower-frequency components. By confining the analysis to the fundamental component, the aZFP should be less subject to distortions in the pressure signal. For each patient, we determined the aZFP at the same two times as described above for the ICAP and MCABV data. The following calculations were performed with the aid of custom software written in MatLab (Mathworks Inc., Natick, MA). To remove high-frequency artifact in the MCABV signal, the ICAP and MCABV waveforms were filtered with a ninth-order finite impulse response low-pass Blackman filter ( $-3$  dB at 3.2 Hz). The start and end of each cardiac cycle were determined from the filtered waveforms and the means (ICAP<sub>0</sub>, MCABV<sub>0</sub>), and fundamental Fourier components (ICAP<sub>1</sub>, MCABV<sub>1</sub>) of ICAP and MCABV in each cardiac cycle were calculated by Fourier transform of the corresponding unfiltered data. The aZFP was calculated by the equation  $aZFP = ICAP_0 - MCABV_0(ICAP_1/MCABV_1)$ .<sup>5</sup> This equation assumes that the relation between ICAP and MCABV is a

straight line that passes through the point (ICAP<sub>0</sub>, MCABV<sub>0</sub>) at a slope of MCABV<sub>1</sub>/ICAP<sub>1</sub>. At each measurement time, the aZFPs for individual cardiac cycles were averaged over either two or three complete respiratory cycles.

#### Statistical Analysis

Results are expressed as mean  $\pm$  SD unless stated otherwise. The two-tailed paired *t* test was used to compare the MAP-ICAP gradient, MCABV, and aZFP at the two times, and  $P < 0.05$  was taken to be statistically significant. A difficulty with this study was that the time available for drug crossover was limited by the duration of carotid clamping, and hence the initial agent was not completely eliminated during the time of data recording. For this reason, the pressure and velocity data for the two groups were analyzed separately.

## Results

Of the 37 cases originally entered into the study, 5 (4 of 17 randomized to the SP group and 1 of 15 randomized to the PS group) had an arterial bypass shunt placed and were therefore excluded. The 32 cases studied included one patient who had bilateral carotid endarterectomies, separated by 4 months, and was studied twice. Before discharge, patients underwent routine neurologic examination by the treating clinician, and no neurologic morbidity was detected in any patient completing the study. The groups were comparable, although the SP group was older ( $P = 0.04$ ): SP group  $73 \pm 7$  yr, 12 males and 3 females; PS group  $66 \pm 11$  yr, 14 males and 3 females.

The time from carotid clamping to commencement of drug crossover was  $7 \pm 3$  and  $9 \pm 4$  min in the SP and PS groups, respectively (table 1). The time between commencement of drug crossover and cessation of ICAP measurement was  $24 \pm 10$  and  $24 \pm 14$  min in the SP and PS groups, respectively. This time was insufficient to allow complete washout of the initial drug, as indicated by the estimated propofol effect site concentration of  $1.1 \pm 0.6$   $\mu$ mol/ml at the end of data collection in the PS group and the end-tidal sevoflurane concentration of  $0.15 \pm 0.1\%$  at the end of data collection in the SP group (table 1).

In the SP group, ICAP increased during crossover between agents (table 2), causing the MAP-ICAP gradient to decrease by a mean of 10 mmHg (95% confidence interval, 6-14;  $P < 0.0001$ ). In no patient in the SP group did the pressure gradient increase, and in 8 of the 17 patients, the pressure gradient decreased by 10 mmHg or more. In the PS group, there was a smaller change in the opposite direction (table 3). The MAP-ICAP gradient increased from  $34 \pm 19$  to  $39 \pm 19$  mmHg, a mean increase of 5 mmHg (95% confidence

**Table 1. Drug Doses and Bispectral Index at Two Times during Carotid Clamping**

Group	SP		PS		
	Time	Drug Crossover	End Data Collection	Drug Crossover	End Data Collection
Time from carotid clamping, min		7 ± 3	31 ± 11	9 ± 4	33 ± 15
Sevoflurane ET, %		1.66 ± 0.4	0.15 ± 0.1	0	1.35 ± 0.4
Propofol Ce, µg/ml		0	3.1 ± 1.1	2.9 ± 0.9	1.1 ± 0.6
BIS		47 ± 5	46 ± 6	49 ± 6	44 ± 9

Data at the time just before initiating drug crossover and at the end of data collection (which occurred with cessation of internal carotid artery pressure measurement). Results are expressed as mean ± SD.

BIS = Bispectral Index; Ce = estimated effect site concentration; ET = end-tidal concentration; PS = group crossed over from propofol to sevoflurane; SP = group crossed over from sevoflurane to propofol.

interval, 2–7 mmHg;  $P = 0.002$ ). In 2 of the 15 patients in this group, the change in gradient was 10 mmHg or more. Figure 1 illustrates recordings from an individual patient in the SP group.

Transcranial Doppler data are incomplete, primarily because of difficulty obtaining and maintaining a reliable signal throughout the period of carotid clamping. In the SP group, changing from sevoflurane to propofol was associated with a significant decrease in ipsilateral MCABV (from  $53 \pm 22$  cm/s to  $43 \pm 17$  cm/s;  $P < 0.001$ ). In the PS group, ipsilateral transcranial Doppler data were only available in five patients, and although there was some increase in ipsilateral MCABV in four of the five, there was no difference in the mean. In the other patient in the PS group (No. 18), ipsilateral MCABV decreased, apparently due to a steal phenomenon; changing from propofol to sevoflurane was associated

with a 39% increase in the contralateral MCABV, a 22% decrease in the ipsilateral MCABV, and a 17% decrease in ICAP (table 3 and fig. 2).

Before calculating the aZFP, we confirmed that the relation between ICAP and MCABV was linear by calculating the correlation coefficient for each cardiac cycle within the respiratory cycles analyzed. After the ICAP data were time-shifted with respect to the velocity data (to account for delay in transmission of the pressure signal), there was a good correlation (median  $r = 0.98$  for all cardiac cycles; interquartile range, 0.96–0.99). Figure 3 depicts the velocity–pressure relation from two individual cardiac cycles from a single patient. The averaged aZFP values, derived from the fundamental components of velocity and pressure, are illustrated graphically in figure 4, and individual aZFP results are presented in figure 5. The mean aZFP

**Table 2. Cerebral Hemodynamic Data in Patients Crossed Over from Sevoflurane to Propofol during Carotid Cross Clamping**

	Sevoflurane					Propofol					$\Delta(\text{MAP-ICAP}),$ mmHg
	MAP, mmHg	ICAP, mmHg	MAP-ICAP, mmHg	MCABV <sub>i</sub> , cm/s	MCABV <sub>c</sub> , cm/s	MAP, mmHg	ICAP, mmHg	MAP-ICAP, mmHg	MCABV <sub>i</sub> , cm/s	MCABV <sub>c</sub> , cm/s	
1	97	28	69	44	66	98	41	57	44	43	-12
2	90	64	26			90	82	8			-18
3	83	52	31	54	35	89	68	21	40	27	-10
4	84	67	17	53	72	83	75	8	45	42	-9
5	84	74	10	83		83	77	6	71		-4
6	92	70	22	51		92	75	17	45		-5
7	99	71	28	38		107	90	17	28		-11
8	80	43	37	112	73	91	65	26	83	45	-11
9	100	90	10	44		105	95	10	35		0
10	91	67	24			101	77	24			0
11	73	59	14	48	54	75	70	5	29	38	-9
12	110	39	71	46		112	70	42	43		-29
13	96	77	19			95	79	16			-3
14	119	61	58			110	79	31			-27
15	89	56	33	45		91	66	25	30		-8
16	90	45	45	48	42	90	51	39	40	39	-6
17	78	56	22	20	26	87	75	12	21	27	-10
<b>Mean</b>	<b>92</b>	<b>60</b>	<b>32</b>	<b>53</b>	<b>53</b>	<b>94</b>	<b>73</b>	<b>21*</b>	<b>43†</b>	<b>37</b>	<b>-10</b>
SD	12	15	19	22	19	10	13	14	17	7.4	8

Changing from sevoflurane to propofol was associated with an increased internal carotid artery pressure (ICAP) and a decreased gradient between systemic arterial pressure and internal carotid artery pressure.

\*  $P < 0.0001$ , †  $P < 0.001$  compared with sevoflurane.

c = contralateral;  $\Delta(\text{MAP-ICAP})$  = change in MAP-ICAP gradient during drug crossover; i = ipsilateral; MCABV = middle cerebral artery blood velocity; MAP = mean radial artery pressure.

**Table 3. Cerebral Hemodynamic Data in Patients Crossed Over from Propofol to Sevoflurane during Carotid Cross Clamping**

	Propofol					Sevoflurane					$\Delta(\text{MAP-ICAP})$ , mmHg
	MAP, mmHg	ICAP, mmHg	MAP-ICAP, mmHg	MCABVi, cm/s	MCABVc, cm/s	MAP, mmHg	ICAP, mmHg	MAP-ICAP, mmHg	MCABVi, cm/s	MCABVc, cm/s	
18	94	59	35	24	31	89	46	43	20	43	8
19	101	74	27			112	81	31			4
20	96	40	56	81	48	92	37	55	84	60	-1
21	98	80	18			106	83	23			5
22	96	88	8			97	86	11			3
23	110	57	53	65		112	46	66	70		13
24	108	47	61		50	113	50	63		40	2
25	96	61	35			87	45	42			7
26	80	74	6			82	70	12			6
27	82	58	24	45	63	82	53	29	47	73	5
28	100	79	21			99	64	35			14
29	105	39	66			107	37	70			4
30	76	56	20	39	25	83	61	22	41	31	2
31	84	31	53			84	30	54			1
32	97	65	32			85	56	29			-3
<b>Mean</b>	<b>95</b>	<b>61</b>	<b>34</b>	<b>51</b>	<b>43</b>	<b>95</b>	<b>56</b>	<b>39*</b>	<b>52</b>	<b>49</b>	<b>5</b>
SD	10	17	19	22	15	12	18	19	25	17	5

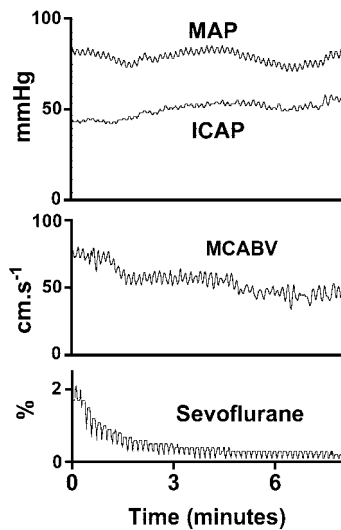
Changing from propofol to sevoflurane was associated with a decreased internal carotid artery pressure (ICAP) and an increased gradient between systemic arterial pressure and internal carotid artery pressure.

\*  $P = 0.002$  compared with propofol.

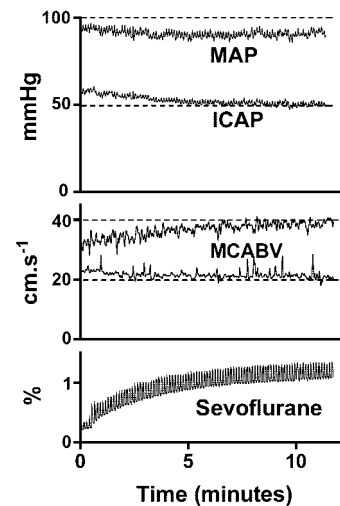
c = contralateral;  $\Delta(\text{MAP-ICAP})$  = change in MAP-ICAP gradient during drug crossover; i = ipsilateral; MAP = mean radial artery pressure; MCABV = middle cerebral artery blood velocity.

of all 18 patients in whom ipsilateral MCABV was available was  $22 \pm 10$  mmHg with sevoflurane and  $30 \pm 13$  mmHg with propofol, a mean difference of 8 mmHg (95% confidence interval, 3-14 mmHg;  $P < 0.01$ ). There was also a difference in slope, defined as

the ratio of the amplitudes of the fundamental components of velocity and pressure ( $\text{MCABV}_i/\text{ICAP}_i$ ). With sevoflurane, the slope was  $1.8 \pm 0.9 \text{ cm} \cdot \text{s}^{-1} \cdot \text{mmHg}^{-1}$ , compared with  $1.4 \pm 0.9 \text{ cm} \cdot \text{s}^{-1} \cdot \text{mmHg}^{-1}$  with propofol ( $P = 0.01$ ).



**Fig. 1.** Changes during the first few minutes after cessation of sevoflurane administration, and simultaneous commencement of propofol infusion in an individual patient (No. 8) during carotid endarterectomy. Changing from sevoflurane to propofol was associated with a decrease in middle cerebral artery blood velocity (MCABV) ipsilateral to the carotid clamping. There was a simultaneous increase in internal carotid artery pressure (ICAP) so that the gradient between ICAP and mean radial arterial pressure (MAP) narrowed. For the purpose of this illustration, the pressure waveforms and MCABV waveform have been smoothed with a low-pass filter.



**Fig. 2.** Changes during the first few minutes after cessation of propofol infusion and simultaneous commencement of sevoflurane administration in an individual patient (No. 18) during carotid endarterectomy. Changing from propofol to sevoflurane was associated with a decrease in internal carotid artery pressure (ICAP) so that the gradient between ICAP and mean arterial pressure (MAP) widened. In this patient, while the middle cerebral artery blood velocity (MCABV) increased on the side contralateral to the carotid surgery (*upper trace*), there was a decrease in MCABV on the ipsilateral side (*lower trace*), indicating a steal phenomenon. For the purpose of this illustration, the pressure and MCABV waveforms have been smoothed with a low-pass filter.

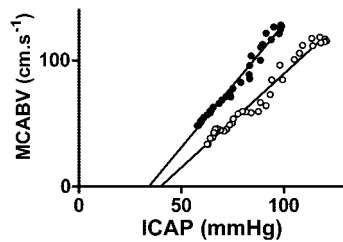


Fig. 3. Plot of middle cerebral artery blood velocity (MCABV) and internal carotid artery pressure (ICAP) from a single patient (No. 5) during carotid clamping. Data are from one cardiac cycle during sevoflurane anesthesia (closed circles) and one cardiac cycle after crossover to propofol anesthesia (open circles). Lines of best fit are also shown ( $r > 0.98$  for both cycles).

## Discussion

In our patients, the gradient between MAP and ICAP during carotid clamping was lower with propofol than with sevoflurane anesthesia, suggesting that cerebral perfusion pressure was better maintained with propofol. The cerebral vasodilating effect of sevoflurane, when compared with propofol, was confirmed during carotid clamping by a lower aZFP, a higher slope of the velocity-pressure relation, and a higher MCABV. Crossing over from sevoflurane to propofol was associated with a decrease in MCABV and a simultaneous increase in ICAP. Crossing over from propofol to sevoflurane led to a decrease in ICAP, although the magnitude of the change was less.

Propofol would not be expected to result in a higher intracranial pressure compared with sevoflurane; propofol decreases intracranial pressure in dogs,<sup>15</sup> and intracranial pressure is lower with propofol than with sevoflurane in humans undergoing craniotomy for brain tumors.<sup>18</sup> Therefore, it is probable that the difference we found in ICAP means that perfusion pressure (defined as the difference between arterial pressure and intracranial pressure) on the side of carotid clamping was higher with propofol than with sevoflurane.

Our finding that MCABV was lower with propofol anesthesia than with sevoflurane anesthesia is consistent

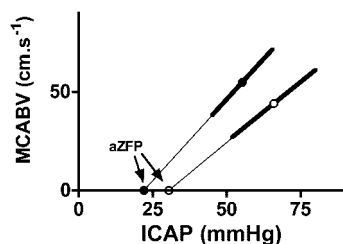


Fig. 4. Average data from 18 patients during carotid clamping. The fundamental (first harmonic) components of middle cerebral artery blood velocity (MCABV) and internal carotid artery pressure (ICAP) were used to calculate the apparent zero flow pressure (aZFP). Heavy lines depict the mean amplitudes of the fundamental components of pressure and velocity. The primary anesthetic agent was either sevoflurane (closed circles) or propofol (open circles). There were statistically significant differences in the aZFP ( $P < 0.01$ ) and the slope ( $P = 0.01$ ).

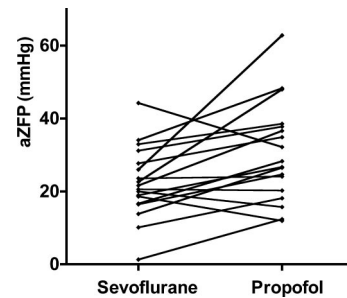


Fig. 5. Individual data for apparent zero flow pressure (aZFP) during carotid clamping with either sevoflurane or propofol as the primary anesthetic agent. Lines connect data points for individual patients.

with the known effects of these drugs on cerebral blood flow (CBF). There is evidence that sevoflurane has intrinsic cerebral vasodilating effects,<sup>14,19,20</sup> and sevoflurane anesthesia does not decrease MCABV below awake values.<sup>21</sup> In contrast, propofol is not associated with cerebral vasodilation; propofol anesthesia reduces MCABV by 26% compared with awake values,<sup>22</sup> and the decrease in CBF matches the propofol-induced reduction in cerebral metabolism.<sup>15,16</sup> Using positron emission tomography in humans, Kaisti *et al.*<sup>20,23</sup> confirmed that propofol and sevoflurane cause similar reductions in cerebral metabolism but CBF and cerebral blood volume are both lower with propofol than with sevoflurane.

We propose that these differences in the cerebrovascular effects of propofol and sevoflurane account for the changes we observed in ICAP. During carotid clamping, blood flow to the ipsilateral side of the circle of Willis is *via* collateral vessels such as the anterior and posterior communicating arteries. These collateral vessels are considered to be conductance vessels, and their resistance is not thought to be altered by factors that change cerebrovascular resistance. Because of the pressure decrease along the collateral vessels, ICAP is usually lower than MAP during carotid clamping. In accord with Ohm's law, if resistance of the collaterals is constant, the pressure decrease along the collaterals (and hence the MAP-ICAP gradient) is proportional to the flow through these vessels. Vasoconstriction of intracerebral arterioles on the side of carotid clamping increases the total resistance to flow, reducing collateral blood flow and thereby reducing the pressure gradient along the collaterals and bringing ICAP closer to MAP. Previously published examples of changes in cerebrovascular resistance leading to changes in ICAP include an increase in ICAP associated with hypocapnia<sup>6</sup> and a decrease in ICAP associated with autoregulatory vasodilation.<sup>7</sup> Similarly, the changes we observed in MAP-ICAP gradient in our patients can be explained by a higher cerebrovascular resistance with propofol compared with sevoflurane.

Intracerebral steal occurs when a cerebral vasodilator increases blood flow to some brain regions but simultaneously decreases flow to a steal-prone region. During

carotid clamping, areas of ipsilateral cortex may become maximally vasodilated if ICAP on the clamped side is below the lower limit of autoregulation. If a cerebral vasodilator then increases flow to other brain regions, causing a further decrease in ICAP, blood flow will decrease in the regions with exhausted vasodilatory reserve. Such steal during carotid occlusion has been described with hypercapnia<sup>24</sup> and inverse steal with hypocapnia.<sup>6</sup> In 11 of our patients, we obtained reliable MCABV recordings bilaterally, and in 1 of those patients, there was evidence of intracerebral steal; changing from propofol to sevoflurane was associated with an increase in the contralateral MCABV and a simultaneous decrease in ICAP. During this time, the ipsilateral MCABV decreased, suggesting that the introduction of sevoflurane led to contralateral cerebral vasodilation, which caused a steal phenomenon. We did not detect steal or inverse steal in the remaining 10 patients in whom bilateral MCABV recordings were available, despite significant changes in ICAP during drug crossover. This observation may indicate that these patients had some cerebral vasodilatory reserve during carotid clamping and were able to further vasodilate when sevoflurane was administered. It should be noted that smaller areas of cerebral steal may have been undetected in some of our patients because transcranial Doppler can only demonstrate steal if it occurs in a substantial proportion of the perfusion territory of the insonated artery.

To our knowledge, this is the first study to report aZFP values during carotid clamping. Our finding that propofol, when compared with sevoflurane, was associated with a higher aZFP and a lower slope of the velocity-pressure relation is consistent with a greater arteriolar tone with propofol. Marval *et al.*<sup>25</sup> compared the changes in aZFP after induction of anesthesia with either sevoflurane or propofol, and they also found aZFP to be greater with propofol than with sevoflurane. A higher aZFP suggests a higher CCP, which, according to the CCP model, indicates a decreased effective perfusion pressure. Interestingly, in our patients, the changes in ICAP and aZFP were in the same direction and of a similar magnitude, and therefore, according to the CCP model, it may be that the higher ICAP with propofol does not represent any net change in effective perfusion pressure.

Most previous studies of aZFP have relied on blood pressure waveforms recorded in an arm, *via* either a radial artery catheter or a finger plethysmographic technique. To accurately define the instantaneous velocity-pressure relation, it would be ideal to measure pressure and velocity in the same vessel, but this is impractical in the case of the MCA in humans. The current study is the first to use ICAP measurements when calculating aZFP, and this experimental design may have advantages because ICAP should more reliably reflect pressure in the insonated vessel. Measuring pressure within the internal

carotid artery minimizes the potential for variability that could arise from differential vasoactive effects of propofol and sevoflurane on the transmission of aortic root pressure to the radial artery. On the other hand, a possible deficiency in our method is that ICAP monitoring was *via* a long embolectomy catheter with an unknown dynamic response that could potentially have distorted the recorded pressure waveform. Such distortion is more likely to have affected the higher frequency components of the waveform, hence our decision to use the amplitude of the fundamental component in the calculation of aZFP. Any distortion in the measuring system that did affect the calculation of aZFP would have been approximately constant throughout the study and hence would not have reduced the validity of the comparison between the two drugs.

Interpretation of our results is affected by the inadequate crossover time for elimination of the initial drug. The time for drug crossover was limited because we did not prolong the period of carotid clamping beyond that required for the surgery. This may have been more of a problem with the PS group because the estimated propofol effect site concentration only decreased by 62%, compared with the 91% decrease in end-tidal sevoflurane in the SP group. However, plasma propofol concentration was not directly measured, and the effect site concentration was estimated by the Diprifusor algorithm based on a particular pharmacokinetic data set that does not account for factors such as the patient's age. It is possible that the difference in the magnitude of ICAP changes between the two groups was due to slower elimination of propofol. Notwithstanding these considerations, our results demonstrate that the effect on MAP-ICAP gradient of changing from propofol to sevoflurane is opposite to the effect of changing from sevoflurane to propofol.

There are several other limitations to our study. The study was restricted to patients in whom we were reasonably certain that CBF was adequate and a shunt was not required; therefore, we have not demonstrated whether the same differences between propofol and sevoflurane occur in patients with more severely compromised collateral perfusion. A higher proportion of the SP group was eliminated from this study because of a decision to use an arterial shunt, although the difference was not significant ( $P = 0.3$ , Fisher exact test). Because a low ICAP was one of the criteria for using a shunt in our patients and because we have demonstrated that sevoflurane is associated with a lower ICAP, it is possible that the four patients eliminated from the SP group included individuals in whom sevoflurane caused a marked decrease in ICAP, and this could have caused the results of our study to underestimate the effect of drug crossover.

It is possible that changing between anesthetic agents caused significant changes in cerebral metabolism that

could have independently influenced CBF. However, we used the BIS to guide anesthetic drug dosage during drug crossover, and positron emission data in humans indicate that, at similar BIS values, there is little difference between propofol and sevoflurane with respect to their suppression of cerebral metabolism.<sup>20</sup> Our study design did not include a control group with no crossover in anesthetic agent, so we cannot exclude the possibility of a time effect whereby ICAP changes during carotid clamping independently of the anesthetic agent. For example, it is possible that the difference in the magnitude of the pressure changes in the two groups could have been due to an underlying tendency for ICAP to decrease during carotid clamping.

We used transcranial Doppler monitoring as an index of changes in CBF. Doppler ultrasound measures blood velocity rather than blood flow, but relative changes in velocity reflect relative changes in flow if the diameter of the insonated vessel is constant. There is evidence that changes in MCABV accurately reflect changes in CBF<sup>26,27</sup>; however, little is known regarding the possible effects on MCA diameter of crossover between the agents used in this study. The assumption that volatile anesthetic agents do not alter MCA diameter has been questioned.<sup>28</sup> If sevoflurane increases MCA diameter compared with propofol, the difference in flow between the two agents may have been greater than that indicated by our MCABV data.

The possible clinical significance of our results is open to interpretation. Of primary importance during carotid clamping is cerebral blood flow, not arterial pressure. Therefore, the decreased MCABV with propofol might suggest that sevoflurane is the preferred agent during carotid clamping. Conversely, if the increased flow with sevoflurane is interpreted as luxury perfusion and if the concomitant lower ICAP can cause steal of flow from areas at risk of ischemia, it could be argued that propofol is the preferred agent. We favor the latter interpretation because, unlike sevoflurane, propofol causes a decrease in CBF that is well matched to cerebral metabolism,<sup>16,20</sup> and the resultant higher perfusion pressure with propofol may preserve flow to areas of brain that have reached their limit of vasodilatory reserve. This interpretation is supported by the observation in one of our patients that changing from propofol to sevoflurane induced interhemispheric steal. The intrinsic cerebral vasodilating effects of volatile agents can be likened to the effect of hypercapnia; historically, hypercapnia was suggested as a method of increasing CBF during carotid clamping until it was demonstrated that hypercapnia reduces ICAP and causes cerebral steal.<sup>6</sup> If ICAP is used to determine the need for a shunt during carotid clamping, it is possible that the lower ICAP with sevoflurane will cause more patients to be shunted with this agent than with propofol.

In conclusion, our data collected during carotid clamping support previous evidence of greater cerebral arteriolar

tone with propofol than with sevoflurane. We found that changing from sevoflurane to propofol reduces the gradient between systemic and internal carotid blood pressures and that changing in the opposite order has the opposite effect. We suggest that these observations may indicate a hemodynamic advantage of propofol anesthesia during carotid clamping, a conclusion that is supported by the steal effect we observed in one patient after changing to sevoflurane. However, currently, there is no outcome-based evidence favoring any particular general anesthetic agent during carotid clamping.

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