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ORIGINAL WORK

Propofol/Remifentanil Anesthesia Might Not Alter the Middle Cerebral Artery Diameter by Digital Subtraction Angiography

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Abstract

Introduction: Transcranial Doppler (TCD) of the middle cerebral artery (MCA) enables the measurement of the mean blood velocity (MCA_{Vm}) and the estimation of the cerebral blood flow (CBF), provided that no significant changes occur in the MCA diameter (MCA_{Diam}). Previous studies described a decrease in the MCA_{Vm} associated with the induction of total intravenous anesthesia (TIVA) by propofol and remifentanil. This decrease in blood velocity might be interpreted as a decrease in the CBF only where the MCA_{Diam} is not modified across TCD examinations.

Methods: In this observational study, we measured the MCA_{Diam} of 24 subjects (almost exclusively females) on digital subtraction angiography under awake and TIVA conditions.

Results: Across the two phases, we observed a decrease in the mean arterial blood pressure (from 84 ± 9 to 71 ± 6 mmHg; $p < 0.001$) and heart rate (76 ± 10 vs. 65 ± 8 beats/min; $p < 0.001$), and a concomitant decrease in the MCA_{Vm} (61 vs. 42 cm/s; $p < 0.001$). In contrast, the MCA_{Diam} did not vary in association with TIVA (2.3 ± 0.2 vs. 2.3 ± 0.2 mm; $p = 0.52$).

Conclusions: Those results suggested that in this population, no significant changes in the MCA_{Diam} are associated with TIVA.

Keywords: Cerebral blood flow, Digital subtraction angiography, Middle cerebral artery, General anesthesia, Transcranial Doppler

Introduction

Regulation of the cerebral blood flow (CBF) is fundamental to supply the brain with oxygen and metabolite substrates according to its needs. In physiological states and within a certain range of arterial blood pressure, constant CBF is maintained by active changes in the vascular tone of the cerebral arterioles (cerebral autoregulation) [1, 2]. Conversely, any pathological event affecting the cardiovascular system or the intracranial pressure has the potential to alter the cerebral circulation and lead to deleterious consequences [3–5]. Therefore, monitoring the CBF is of great relevance in the management of patients with cerebral impairment or hemodynamic instability in order to maintain the appropriate oxygen supply to the brain during any condition.

Transcranial Doppler (TCD) is a noninvasive bedside tool that enables the indirect assessment of the CBF [6]. TCD measures the blood velocity in single, large, proximal cerebral arteries (i.e., components of

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the Willis circle) [7]. The middle cerebral artery (MCA) is the most frequently insonated intracranial vessel because it is easily delineated through the temporal window. Moreover, as the MCA collects approximately 70% of the internal carotid artery (ICA) blood flow, it is usually considered representative of the total blood flow to its ipsilateral hemisphere. Thus, TCD has been developed in the evaluation and management of multiple cerebral pathologies, such as traumatic brain injury and subarachnoid hemorrhage, and for the diagnosis of brain death [8–11]. Mean blood velocity (MCA_{Vm}) appears to be a strong surrogate for the CBF in healthy subjects, although correlations are weaker in specific brain pathologies [12]. Although the MCA blood flow (MCA_{Flow}) is directly related to the cross-sectional area of the insonated artery, the MCA_{Vm} can be differently modified in the presence of variations in the MCA diameter (MCA_{Diam}), such as during cerebral vasospasm [7]. This variation constitutes one of the main issues when using the MCA_{Vm} as a surrogate for the CBF, as any undetected changes in the MCA_{Diam} might lead to deceptive interpretations [13]. Direct intraoperative measurements have shown that the MCA_{Diam} did not significantly change according to variations in mean arterial pressure (MAP) or $PaCO_2$ [14]. Conversely, a recent study showed a 2% decrease in the MCA cross-sectional area measured by magnetic resonance imaging (MRI) during rhythmic handgrip exercise, prompting sympathetic control of large cerebral arteries [15].

Anesthetic agents have variable effects on global CBF, cerebral blood volume, and cerebral metabolism ($CMRO_2$), but the mechanisms by which these agents induce such alterations are still poorly understood. Volatile anesthesia has direct cerebral vasodilation, but is not associated with MCA_{Vm} changes, suggesting that its activity is likely exerted downstream of the main stem MCA level [16, 17]. In contrast, propofol has been recommended as the hypnotic agent of choice in the neurocritical care setting, although it is associated with a significant decrease in the MCA_{Vm} [18]. Indeed, in healthy subjects, a graded and significant reduction in the MCA_{Vm} is observed when target doses of propofol are increased [16]. This MCA_{Vm} decrease is accompanied by a decrease in $CMRO_2$ [18] and in the CBF, but it remains to be determined if that can be explained by a decrease in upstream blood pressure, by a vasoconstriction at the MCA main stem level or by regulation occurring more downstream. If the MCA_{Diam} is modified in association with propofol exposure, the MCA_{Vm} might no longer reflect the MCA_{Flow}. Indirect measurements by the analysis of the reflected Doppler signal power have suggested that the MCA cross-sectional area is unlikely to be influenced by different intravenous hypnotics, including propofol [19]. Furthermore, in animal models of isolated vessels, no direct vasoactive effects of propofol have been demonstrated [20, 21]. Nevertheless, in vivo MCA_{Diam} modifications by direct measurements associated with propofol anesthesia have never been properly investigated.

Digital subtraction angiography (DSA) is a computer-assisted radiographic visualization of cerebral vessels. Images are produced using contrast medium by subtracting a "precontrast image" from subsequent images. Currently, DSA constitutes the most precise tool to detect neurovascular alterations and is the gold standard for intracranial aneurysm assessment [22].

The main purpose of the present study was to measure the MCA_{Diam} by DSA in a given population under total intravenous anesthesia (TIVA) by propofol and remifentanil and to compare this value to the MCA_{Diam} observed during awake conditions. Second, we aimed to describe MCA_{Vm} variations across TIVA induction.

Materials and Methods

Participants

From an institutional database, we performed a retrospective analysis of prospectively collected data. All consecutive patients who underwent a transverse sinus stenting in the interventional neuroradiology department of Lariboisière University Hospital (Paris, France) between December 2014 and May 2017 have been recruited. Patients were selected for a transverse sinus stenting when they had a disabling pulsatile tinnitus or intracranial hypertension detected by the presence of a papillary edema at fundus oculi examination or by brain MRI (empty sella turcica, widening of optic nerves sheaths, and tortuosity of the optic nerves). Exclusion criteria were age < 18 years, hemodynamic impairment, or any organ failure. For each patient, we recorded demographics, diagnosis at admission, past medical history, treatment, and perioperative data. Arterial hypertension was defined by a systolic blood pressure (SBP) > 130 mmHg or a diastolic blood pressure (DBP) > 90 mmHg. Pathologic obesity was defined by a body mass index (BMI) > 30 kg/m^2.

Ethical approval for this study was provided by the Ethical Committee of the Institutional Review Board of the *Société de Réanimation de Langue Française* (CE SRLF 11-356 and CE SRLF 14-34). Patient consent was waived.

Neuroradiological Procedure and Cerebral Venous Pressure Measurement During Transverse Sinus Stenting

The angiography was obtained by hand injection of approximately 5 ml of Xenetix® iodine 350 mg/ml into the ICA selective catheterization. In some cases, the measurement of the pressure within the venous sinuses was made through a cerebral angiography during awake conditions. In particular, the venous pressure in the superior sagittal sinus (P_{sss}) upstream of the transverse sinus stenosis, and in the sigmoid sinus downstream of the stenosis, was recorded (see previous publication) [19]. When an awake phase was not considered necessary, the pressure measurement was made only after induction of TIVA. The stenting was always positioned under TIVA.

Conduct of Anesthesia

No pre-anesthesia medication was given. TIVA was induced either before the femoral artery catheterization or later, once venous sinuses pressure had been recorded. Every time, TIVA was induced with propofol and remifentanil target-controlled infusion. Tracheal intubation was facilitated with atracurium 0.5 mg kg^{-1}, and mechanical ventilation with volume-controlled mode was used with tidal volumes of 7 ml kg^{-1}, a positive end-expiratory pressure of 5 cm H_2O, and a respiratory rate of 12–16 breaths min^{-1} to maintain an end-tidal pressure of CO_2 ($EtCO_2$) of 32–38 mm Hg. Bispectral index (BIS) was used to target anesthesia depth (objective 30–60). Low continuous doses of noradrenaline have been used to keep a MAP above 65 mmHg or 80% of basal value (see previous publication) [23]. MAP, SBP, DBP noninvasive arterial blood pressure, and heart rate (HR) have been collected.

Measurement of MCA_{Diam}

The MCA_{Diam} by DSA under TIVA was measured for all the originally screened patients undergoing a transverse sinus stenting. The measurements were performed on the clearest image of the MCA in the anterior–posterior plan from its internal carotid origin to its branching, on the ipsilateral hemisphere of the transverse sinus to treat. The measurements were performed in three segments, one proximal after the start of the anterior cerebral artery, one distal before the bifurcation, and one in between those two positions. After excluding different behaviors of singular MCA segments, an average of those three values was calculated and used for the ensuing analysis. An example of the three segments measurement method is outlined in Fig. 1. The basal value of the MCA_{Diam} was evaluated according to patient age (according to previous literature, the population was split into two groups: younger and older than 40 years) [24] and hemisphere side.

Some patients among the initially recruited population had DSA before induction of TIVA for cerebral vessel pressure measurements. We selected those patients to determine the MCA_{Diam} modifications associated with TIVA. For each measure of interest, the intrinsic intra-reader and inter-reader reproducibility was assessed.

TCD Examination and Flow Assessment

Whenever possible, TCD examinations were performed before and after the induction of TIVA by using two pulsed 2-MHz TCD ultrasound probes (Atys Medical©, Lyon, France). Identification of the MCA_{Vm} was confirmed using standard criteria at a depth of 45–55 mm. The same individual performed the two examinations in order to avoid inter-operator biases. Peak systolic velocity (MCA_{Vs}), mean velocity (MCA_{Vm}), end diastolic velocity (MCA_{Vd}), and pulsatility index (PI) were collected before and after the induction of TIVA in the moment of the respective DSA sequence.

We calculated off-line the MCA_{Flow} by multiplying the MCA_{Vm} by the surface of the MCA section (MCA_{sect}). The MCA_{sect} was obtained from the MCA_{Diam} assuming a circular cross section.

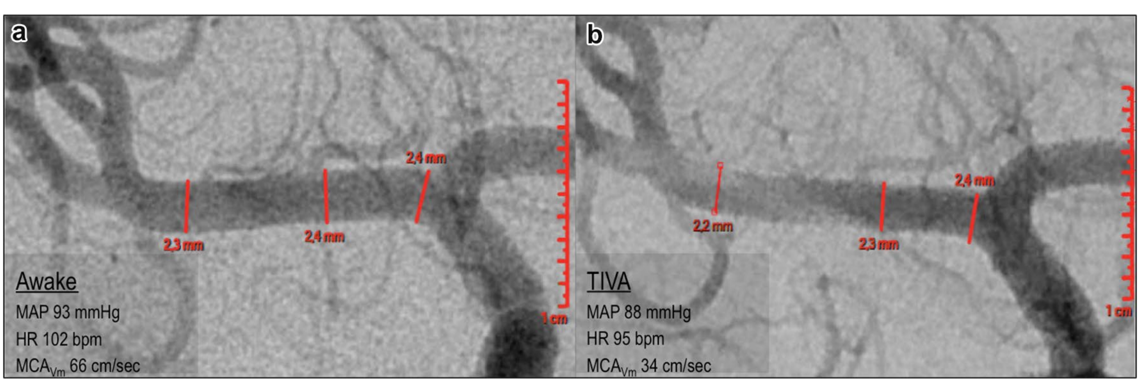

Fig. 1 DSA measurement of the right MCA_{Diam} of a patient undergoing a transverse sinus stenting before (**a**) and after (**b**) induction of TIVA. *MAP* mean arterial pressure, *HR* heart rate, *MCA_{Vm}* mean velocity through MCA

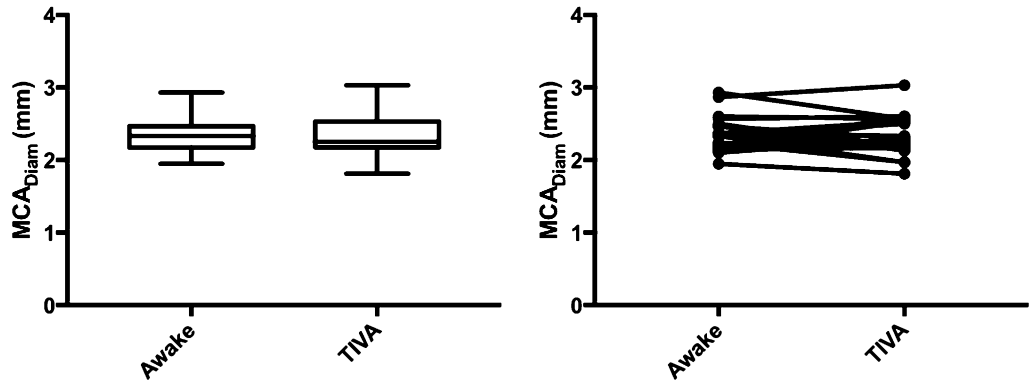

Fig. 2 MCA_{Diam} before and after the induction of TIVA ($n = 24$)

Statistical Analysis

Statistical analyses were performed with GraphPad Prism 5.0 (GraphPad Software, Inc., San Diego, CA). Categorical variables were described in terms of frequencies and percentages, and continuous variables were described in terms of mean values and standard deviations. A nonparametric test Mann–Whitney was used to compare the MCA_{Diam} according to age, and a nonparametric Wilcoxon rank test to track variations in the MCA_{Diam} before and after induction of anesthesia. A p value of < 0.05 was considered significant.

For each measure of interest, the intrinsic intra-reader and inter-reader reproducibility was assessed from the corresponding repeated measurements using Bland–Altman analysis, designed to quantify a systematic difference (bias) between two measurements, as well as the spread of differences in individual pairs of measurements (limits of agreement) and intraclass correlation coefficient (ICC) with 95% confidence intervals [25]. All analyses were performed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria) [26].

Results

MCA_{Diam} Measurement in DSA During TIVA

Sixty-seven patients underwent a stenting of the transverse sinus between 2012 and 2017. The characteristics of the patients are listed in Table 1. Patients were almost exclusively female (97%), relatively young (41 ± 14 years old) and with few comorbidities (American Society of Anesthesiologists score 1 or 2), mainly pathologic obesity (37%) and treated arterial hypertension (18%). Hemodynamic and other perioperative data were largely within normal range.

Measurements of the three segments of the MCA were made for each patient. The mean value of the MCA_{Diam} was 2.4 ± 0.3 mm. A reduction in the MCA_{Diam} was observed moving along the M1 tract from its origin to its branching; the proximal segment measured 2.5 ± 0.3 mm, the middle measured 2.4 ± 0.3 mm, and the distal measured 2.3 ± 0.3 mm. The average MCA_{Diam} was 2.4 ± 0.2 mm in the group of patients younger than 40 years old ($n = 34$) and was 2.5 ± 0.3 mm in the group of patients older than 40 years old ($n = 33$), a difference trending toward significance ($p = 0.066$). Twenty-six

Table 1 Characteristics of the population of patients undergoing a transverse sinus stenting under TIVA

N = 67	Mean ± SD
Age (years)	41 ± 14
Female, *n* (%)	65 (97%)
BMI (Kg/m^2)	28 ± 7
ASA score	2 ± 1
Comorbidities	
Arterial hypertension, *n* (%)	12 (18%)
Obesity, *n* (%)	25 (37%)
Intracranial hypertension, *n* (%)	29 (43%)
Physiological parameters during TIVA	
MAP (mmHg)	70 ± 7
HR (beats/min)	63 ± 10
$EtCO_2$	34 ± 2
SpO_2 (%)	99 ± 1
BIS index	31 ± 8
Intravenous drugs	
Propofol target concentration (mcg/ml)	4.2 ± 2
Remifentanil target concentration (ng/ml)	4.3 ± 5
Norepinephrine (mcg/kg/min)[a] *n* = 41	0.008 ± 0.01
MCA_{Diam}	2.4 ± 0.3 mm

See text for details

ASA American Society of Anesthesiologists (Physical Status Classification Scale), *BIS* bispectral index, *BMI* body mass index, *$EtCO_2$* end-tidal pressure of CO_2, *HR* heart rate, *MAP* mean arterial pressure, *MCA_{Diam}* MCA diameter, *SpO_2* peripheral oxygen saturation, *TIVA* total intravenous anesthesia

[a] Dose necessary to keep MAP > 65 mmHg

patients needed 0.008 ± 0.01 mcg/kg/min noradrenaline to maintain MA$p > 65$ mmHg; between the group needing noradrenaline and the control group, the MCA_{Diam} was comparable ($p = 0.32$).

MCA_{Diam} Before and After Induction of TIVA

Among those 67 patients, 24 patients had a DSA during awake conditions and subsequently, after the induction of TIVA. The time that passed between the two time points was 28 ± 11 min. A decrease in the MAP from 84 ± 9 to 71 ± 6 mmHg ($p < 0.001$) and the HR from 76 ± 10 beats/min to 65 ± 8 beats/min ($p < 0.001$) was observed between the two DSA. During TIVA DSA, a sufficient suppression of consciousness (BIS index of 33 ± 7) was maintained with a target concentration of propofol of 4.5 ± 1.3 mcg/ml and remifentanil of 4.9 ± 2.4 ng/ml; mean $EtCO_2$ was 34 ± 1 mmHg (Table 1).

During awake DSA and TIVA DSA, the MCA_{Diam} consistently measured 2.3 ± 0.2 mm ($p = 0.6$) in awake and TIVA conditions (Fig. 2).

MCA_{Vm} and MCA_{Flow} Before and After Induction of TIVA

For 12 of the 24 patients, TCD was performed before and after the induction of TIVA, and a reduction in blood velocities was clearly delineated (Table 2). The MCA_{Vm} decreased from 54 ± 11 to 36 ± 10 cm/s (33% decrease, $p < 0.001$) (Fig. 3), the MCA_{Vs} decreased from 82 ± 16 to 62 ± 15 cm/s ($p < 0.001$), and the MCA_{Vd} decreased from 41 ± 10 to 23 ± 8 cm/s ($p < 0.001$). The PI increased from 0.8 ± 0.2 to 1.2 ± 0.3 ($p = 0.002$). The MAP decreased from 87 ± 9 to 68 ± 4 mmHg (17%, $p < 0.001$). The MCA_{Diam} was unchanged (2.3 ± 0.2 mm before and after induction of TIVA, $p = 0.6$). The MCA_{Flow} decreased from 152 ± 41 ml/min to 100 ± 26 ml/min after the induction of TIVA ($p < 0.001$).

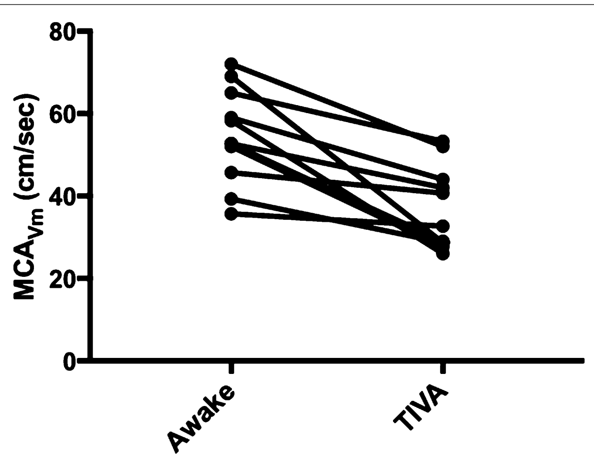

Fig. 3 MCA_{Vm} before and after the induction of TIVA ($n = 12$)

Table 2 Hemodynamics, TCD, and DSA parameters before and after induction of TIVA

$N = 24$	Awake (mean ± SD)	TIVA (mean ± SD)	*p* value
MAP (mmHg)	84 ± 9	71 ± 6	< 0.001
HR (bpm)	76 ± 10	65 ± 8	< 0.001
$EtCO_2$ (mmHg)	NA	33 ± 2	
BIS index	98 ± 1	33 ± 6	< 0.001
SpO_2 (%)	99 ± 1	99 ± 1	
MCA_{Diam} (mm)	2.3 ± 0.2	2.3 ± 0.2	$p = 0.6$
MCA_{Sect} (mm^2)	4.4 ± 1	4.3 ± 1	$p = 0.7$
MCA_{Vm} (cm/s)[a]	54 ± 11	36 ± 10	< 0.001
MCA_{Vs} (cm/s)[a]	82 ± 16	62 ± 15	< 0.001
MCA_{Vd} (cm/s)[a]	41 ± 10	23 ± 8	< 0.001
Pulsatility index (PI)[a]	0.8 ± 0.2	1.2 ± 0.3	$p = 0.002$
MCA_{Flow} (ml/min)[a]	152 ± 41	100 ± 26	< 0.001
P_{sss} (mmHg)	22 ± 6	17 ± 6	< 0.001

BIS bispectral index, *DSA* digital subtraction angiography, *$EtCO_2$* end-tidal pressure of CO_2, *HR* heart rate, *MAP* mean arterial pressure, *MCA_{Vm}* mean blood velocity through MCA, *MCA_{Vs}* systolic blood velocity through MCA, *MCA_{Vd}* diastolic blood velocity through MCA, *MCA_{Flow}* mean blood flow through MCA, *P_{sss}* venous blood pressure in the superior sagittal sinus, *SpO_2* peripheral oxygen saturation, *TCD* transcranial doppler, *TIVA* total intravenous anesthesia

[a] $N = 12$

DSA Intrinsic Intra-reader and Inter-reader Reproducibility

The MCA_{Diam} was measured in the proximal, middle, and distal M1 tract. Those three measurements were made during awake DSA and TIVA DSA for 24 patients (3 × 2 × 24 = 144 measurements). The main observer (SAM) and VC repeated all measurements blinded to the previous measurements. For each measurement, for their before–after TIVA induction mean values and before–after deltas, the intrinsic intra-reader and inter-reader reproducibility was assessed. All measured parameters showed a high reproducibility, as ICCs were consistently > 0.8. Intra-observer before–after deltas bias was 0.01 mm (limits of agreement [− 0.21 to 0.22]; ICC 0.84 [0.67–0.93]). Inter-observer before–after deltas bias was − 0.01 mm (limits of agreement [− 0.22 to 0.21]; ICC 0.85 [0.72–0.91].

Discussion

The results of this study, performed on a population undergoing a transverse sinus stenting, can be summarized as follows: (1) The MCA_{Diam} measured approximately 2.4 ± 0.3 mm under TIVA by propofol and remifentanil ($n = 67$), (2) the MCA_{Diam} remained unchanged during TIVA in comparison with basal awake conditions ($n = 24$), and (3) the MCA_{Vm} measured by TCD decreased by approximately 35% during TIVA ($n = 12$). Our measurements of the MCA_{Diam} were performed on DSA by two observers; intra-reader and inter-reader reproducibility was satisfying.

In a population of 67 almost exclusively female patients undergoing a transverse sinus stenting, the MCA_{Diam} measured 2.4 ± 0.3 mm. In particular, the MCA_{Diam} measured 2.3 ± 0.2 mm in patients younger than 40 years old and 2.5 ± 0.3 mm in patients older than 40 years old; no differences were found between the left and right MCA_{Diam}. Our results are consistent with the DSA measurements of the MCA by Tarasów et al. [24] (2.45 ± 0.9 mm in men and 2.36 ± 0.8 in women). By high-resolution MRI of awake patients, Verbree et al. [15] measured a MCA_{Diam} of 3.1 mm (corresponding to a cross-sectional MCA area of 7.47 mm^2), while Serrador et al. [27] measured a mean MCA_{Diam} of 2.9 mm. In the present study, MCA_{Diam} at the origin of the vessel was 2.5 ± 0.3 mm, but the population was mainly composed of young females. A comparison between the MCA_{Diam} on MRI and DSA should be specifically investigated.

The most important finding of this study is that propofol/remifentanil anesthesia was not associated with significant changes in MCA_{Diam} in a cohort of 24 patients undergoing a transverse sinus stenting. In previous studies, the MAP and $PaCO_2$ changes had not been associated with MCA_{Diam} variations measured by MRI in awake patients [27] and by direct measurements during craniotomies in generally anesthetized patients [14]. Furthermore, the MCA cross-sectional area by indirect measurement from TCD appeared to not be influenced by different intravenous hypnotics, including propofol [19]. Nevertheless, to the best of our knowledge, the MCA_{Diam} modifications, by direct measurement, associated with TIVA had never been specifically investigated. By excluding significant MCA_{Diam} changes before and after TIVA induction, we can draw the insight that the MCA_{Vm} across TIVA actually reflects the MCA_{Flow}.

For 12 of the 24 patients for whom awake and TIVA angiography was available, a TCD was performed before and after induction of anesthesia. Consistent with the findings of other groups [16], we observed a reduction of approximately 35% of the MCA_{Vm} between the two time points. As we did not observe a concomitant change in the MCA_{Diam}, we can assume that the TCD actually detected the reduction in MCA_{Flow} associated with TIVA.

Verbree et al. [15] suggested that a 2% reduction of the MCA cross-sectional area is seen in response to sympathetic activation and concluded that the CBF could be overestimated when using TCD. The corresponding reduction in MCA_{Diam} was only 0.033 mm (1.1%). We think that those small changes could be clinically negligible compared to the reduction in intra-vessel velocities during TIVA induction.

Propofol is known to decrease blood pressure and cardiac output by approximately 30% and 40%, respectively, after an induction infusion dose of 0.50–0.75 mg kg^{-1} min^{-1} [28]. On the other hand, propofol also decreases brain metabolism in every region of the brain by 30–70% at loss of consciousness [29]. However, whether propofol reduces flow and metabolism in equivalent proportions is still not well determined [30, 31]. Several studies suggested that the CBF decrease associated with propofol anesthesia was more significant than the decrease in $CMRO_2$, concluding that propofol might have direct cerebral vasoconstricting activity [32, 33]. Nonetheless, direct vasoconstricting effects of propofol on cerebral arteries in animal studies have not been observed [20, 21]. Our findings suggest that propofol does not exert a vasoconstrictive effect at the MCA level. However, considering that $EtCO_2$ was maintained within a normal range (although at its low end frame), the MAP was maintained above 80% from basal values, and that autoregulation was intact in this patient population, we can deduce that TIVA was associated with vasoconstriction downstream of the MCA level. This explanation would be compatible with a metabolic coupling effect, and future investigations should integrate more peripheral cerebral perfusion monitoring (i.e., near-infrared spectroscopy) to better clarify this question. It is known that the addition of remifentanil to propofol causes a greater reduction of the MAP and the HR, but does not appear to affect the MCA_{Vm} [34, 35], except when used at very large doses for cardiac surgery [36]. The particular effect of propofol on the MCA_{Diam} has not yet been investigated, but a specific effect of remifentanil over propofol cannot be outlined in the present study.

Several limitations to the present research can be noted. The main outcome was MCA_{Diam} measurement before and after induction of anesthesia. These data were obtained retrospectively for 24 consecutively treated patients for whom DSA was performed under awake and general anesthesia conditions. Although measurements have been made in a retrospective manner, patient selection bias was likely avoided as all consecutive patients treated in such a way were selected. Many of those patients were also included in a previous study comparing trans-stenotic venous pressure gradient before and after induction of anesthesia [37]. A secondary outcome was the MCA_{Vm} measurement before and after induction of anesthesia. This measurement was realized to calculate the MCA_{Flow} in a sample of patients. As TCD measurements were not available for all 24 previously included patients, we retrospectively selected for this descriptive analysis only the 12 patients among the previous 24 for whom a TCD was performed. The detection of the MCA_{Vm} variations associated with anesthesia was not a purpose of the present research, and we believe that a prospective study is necessary to verify this issue.

The sample size is too restricted to draw definitive conclusions. Our population was almost exclusively composed of females, and no conclusions can be then extended to male patients, especially as a higher sympathetic reactivity of the MCA might be characteristic of male individuals [15]. Nonetheless, the population of this study is very homogenous and composed of healthy individuals; we deem that this constitutes a suitable model for assessing the own effect of TIVA on MCA_{Diam}.

We cannot confidently exclude that smaller changes in the MCA_{Diam} could be hidden by the resolution of DSA images. Of note, intra-rater and inter-rater variability has been excluded. Furthermore, smaller modifications of the MCA_{Diam} would not influence our conclusions, as they would not implicate significant variations of MCA_{Flow}.

The time between awake and TIVA DSA was 28 min, but the time between induction of TIVA and the second DSA was shorter. Nevertheless, induction of TIVA and DSA were not concomitant, and compensatory mechanisms could have taken place within those minutes. Furthermore, the cerebral venous pathology of those patients might have theoretically affected their upstream arterial circulation. However, all measurements were performed before the sinus stenting procedure, and hence, similar conditions were ensured across the two time points DSA. We acknowledge that cerebral venous stenting is not a routine practice in other centers, and the present findings will therefore need to be confirmed in more common clinical situations. Of note, the anesthesia induction has been performed according to a common standard of care for neurological procedures; in particular, the $EtCO_2$ and the MAP were always maintained within normal ranges. Regrettably, $PaCO_2$ was not monitored before induction of TIVA, and there was no information about the real $PaCO_2$ during the anesthesia phase. Under TIVA, the $EtCO_2$ was at the lower end of the normal range (33 ± 2 mmHg), potentially inducing a slight vasoconstriction of cerebral vessels, but most likely $PaCO_2$ was normal and similar to its basal value as all patients were free from hemodynamic or respiratory impairment. Similarly, the MAP decreased between the two time points (84 ± 9 mmHg to 71 ± 6), but was maintained above 80% of its basal value. It would have been interesting to research possible variations in the MCA_{Diam} associated with noradrenaline; unfortunately, DSA images before and after the introduction of vasopressors were not available, and moreover, noradrenaline doses were very low (0.008 ± 0.1 mcg/kg/min).

Ultimately, only general anesthesia with propofol and remifentanil was tested, and no conclusions can be broadened to the use of other hypnotics. Anesthetic gases, for instance, likely induce a vasodilation at the MCA level [17, 38]; in the future, direct observation by DSA would allow us to verify this hypothesis.

Conclusions

In summary, these findings in a small and selected almost exclusively female and healthy population suggest that no significant changes in MCA_{Diam} are associated with total intravenous propofol/remifentanil anesthesia. Thus, in this cohort, TCD might reliably estimate the MCA_{Flow}, and likely the CBF, under TIVA. Further studies will be necessary to confirm whether TIVA is also not associated with the MCA_{Diam} changes in patients with different characteristics, especially in male individuals and in brain-damaged patients. Indeed, reliability of TCD under anesthesia is mostly useful in a neurocritical care setting. Microcirculation monitoring in association with TCD will be useful to confirm the idea that the regulation of the CBF during anesthesia occurs downstream of the main stem MCA level.

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Author Contributions

SAM contributed to original idea, patients' recruitment, data collection, arterial diameter measurements, statistic analysis, and manuscript writing. NE contributed to original idea, study design, and manuscript writing. VC performed neuroradiological procedures, venous pressure and arterial diameters measurements, and critical revision. JM contributed to critical revision. MAL performed neuroradiological procedures and venous pressure measurements and critical revision. JPSM performed neuroradiological procedures and pressure measurements and critical revision. AM contributed to critical revision and project supervision. EG contributed to critical revision and project supervision. EH performed neuroradiological procedures and pressure measurements and critical revision. FV contributed to original idea, study design and direction, and manuscript writing.

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Conflict of interest

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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