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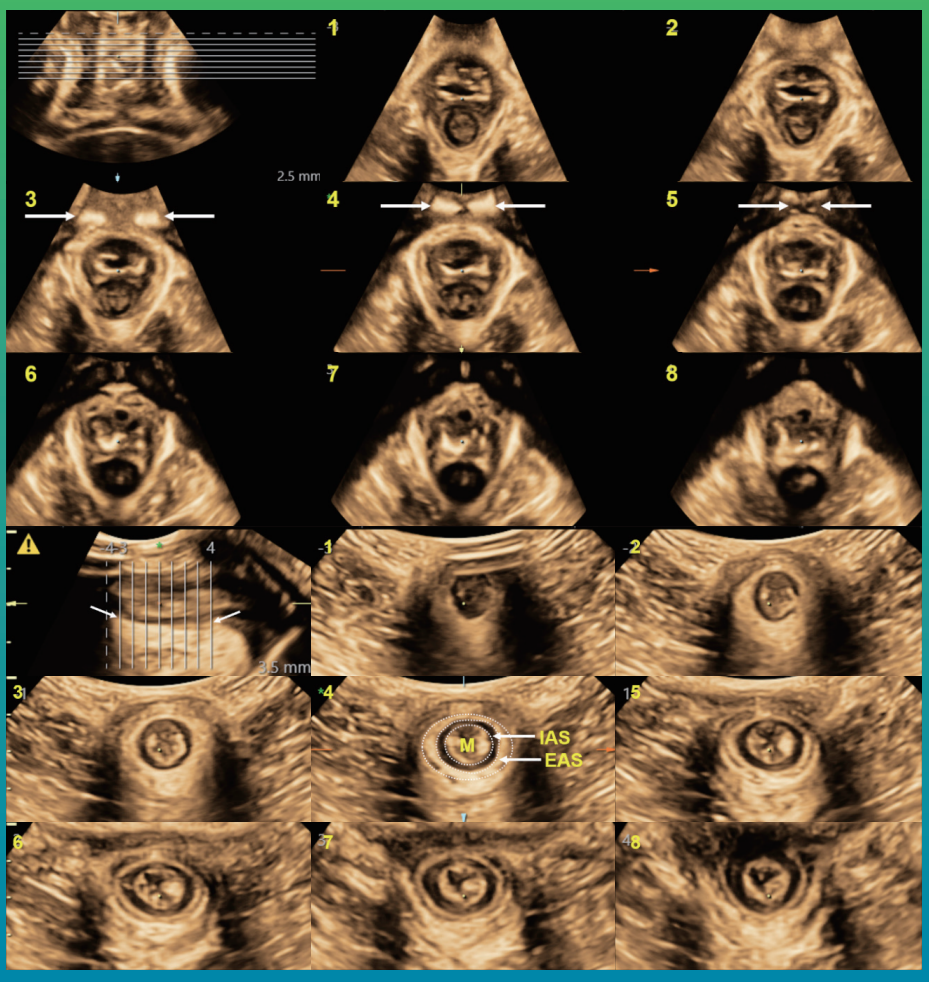

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ORIGINAL RESEARCH

Decreased Cerebral Flow Velocities from General Anesthesia are Not Associated with Cerebral Hyperperfusion Syndrome

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Objective: General anesthesia (GA) can decrease cerebral flow velocities and predispose patients to cerebral hyperperfusion syndrome (CHS) and other perioperative adverse events after carotid endarterectomy (CEA). The aim of this study was to investigate whether decreased pre-operative flow velocity is associated with an increased risk of CHS and perioperative cerebral infarct, and to further identify risk factors if there is any.

Methods: We retrospectively evaluated 920 consecutive patients who received CEA from 2010 to 2020 at a major academic hospital in China. Middle cerebral artery (MCA) blood flow velocities were measured before and after induction of the GA by transcranial Doppler (TCD). Patients were classified into two groups: the NORMAL group if flow velocity decreased < 30% and the LOW group if flow velocity decreased ⩾30%. The ultrasonographic diagnostic criterion of CHS was defined as the 100% increase in flow velocity by TCD from the baseline to post-CEA. The occurrence of CHS, perioperative cerebral infarction was compared between the two groups.

Results: 399 (43.4%) were classified as LOW measurement, and 521 (56.6%) patients were classified as NORMAL measurement. In the LOW group, there were more patients with diabetes, fewer patients with ipsilateral ICA severe stenosis and the opening of anterior/posterior communicating artery. Although the occurrence of CHS per ultrasonography criteria was higher in the LOW group (21.3% vs 15.7%, $P = 0.03$), the occurrence of CHS per clinical criteria (3.2%, vs 2.1%, $P = 0.28$) or the perioperative cerebral infarct between the two groups (5.8% vs 5.0%, $P = 0.60$) is equivalent.

Conclusion: Patients with decreased flow velocities post-GA were more likely to meet the ultrasonography criteria for CHS, but they are not at risk of developing clinical CHS or perioperative cerebral infarct.

Key words: Hyperperfusion; Carotid endarterectomy; Transcranial Doppler; Anesthesia; Brain blood flow

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Carotid endarterectomy (CEA) is considered as the standard treatment for symptomatic extracranial carotid artery stenosis [1]. Cerebral hyperperfusion syndrome (CHS) is a post-operative complication of CEA. Although the incidence of CHS is only 0-3%, it is a severe and catastrophic event which most surgeons try to prevent. CHS is clinically characterized by moderate to severe headache, vomiting, seizures, intracerebral or subarachnoid haemorrhage [2]. Quantitatively, the most acceptable definition of

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hyperperfusion as ⩾ 100% increase in cerebral blood flow (CBF) compared with the baseline as measured by transcranial Doppler (TCD) which predicts the subsequent risk of the CHS [3].

Several conditions were considered as potential risk factors including preoperative, intraoperative and postoperative such as recent cerebral infarction, contralateral occlusion, hypertension, high-grade carotid stenosis, and impaired cerebrovascular reserve. Among these, impaired cerebral autoregulation is one of the most important mechanisms of CHS [2]. The mean blood flow velocities (MV) of the ipsilateral middle cerebral artery (MCA) become blood pressure (BP) dependent during CEA regardless CBF beyond the autoregulation range (60-160 mmHg) when it was impaired. Additionally, the rising concentration of carbon dioxide (CO_2) can disrupt the autoregulation [4] which may predispose to CHS.

CEA can be done with local anesthesia or general anesthesia (GA). Various anesthetic drugs have different impact on the cerebral autoregulation. TCD is commonly used as a monitoring tool during CEA as it can measure the MCA blood flow velocity continuously in real time. After induction of GA, the brain blood flow velocities are reduced accordingly as BP decrease and heart rate (HR) slows down. Typically, the MCA flow velocity does not decrease > 30% after GA [5].

There were several prior studies investigating the association of increased MCA velocity and risk of CHS [6-8]. However, they used the preoperative awaking blood velocity as the baseline rather than the blood velocity after the induction of GA which could lead to fewer patients meeting the criteria of "hyperperfusion". Newman et al. showed only 1.1% of patients who underwent CEA from 1995-2007 without guidance for managing CHS suffered a stroke due to CHS and 0.0% of patients who underwent CEA from 2008-2012 after the guideline for treating CHS were available [6]. Concerns were raised that we could fail to identify patients at potential risk for CHS.

The aim of this study was (1) to investigate whether decreased MCA blood flow after induction of GA is associated with an increased risk of "hyperperfusion" by ultrasound criteria and CHS by clinical criteria; (2) to investigate whether decreased MCA flow velocity is also associated with perioperative cerebral infarct; and (3) to identify potential factors associated with decreased MCA blood flow from GA.

Materials and Methods

Patients

The study protocol was approved by the Institutional Review Board of Xuanwu Hospital. From January 2010 to May 2020, a total of 1,238 patients with carotid artery stenosis (asymptomatic and symptomatic) underwent CEA in our academic hospital. All these patients were evaluated extra- and intracranial arteries and collateral circulation by color Doppler ultrasound (CDU), TCD and further confirmed by digital subtraction angiography (DSA) before undergoing CEA. 920 out of 1238 patients have good temporal windows and have completed TCD data. Additionally, they all had magnetic resonance imaging (MRI) and/or computed tomography (CT) before and after the procedure to determine the presence of perioperative ischemic infarct.

TCD procedure

Cerebral flow velocities were measured before, during and after the operation with 1.6-2.0 MHz transducer with pulsed TCD device (EMS-9PB, Inc. Delica, China). The scale, gain, and gate of the waveform was set to sample an optimal signal of the main stem of MCA from 50-60 mm according to the head size of patients. The following hemodynamic parameters were measured: the peak velocity, diastolic velocity, mean velocity and pulsatility index (PI) of both hemispheric vessels including MCA, the terminal segment of internal carotid artery (TICA), anterior cerebral artery (ACA) and posterior cerebral artery (PCA) before and after the procedure.

The head with a frame was fixed during the operation to better monitor the blood flow of bilateral MCA. Velocities of MCA were measured before and after induction of the GA when BP and HR keep stable. The parameters were also recorded at the stage of pre-clamp and 5minutes within de-clamp of the carotid artery (Fig. 1). The mean artery pressure (MAP), HR and carbon dioxide pressure (PCO_2) were recorded synchronously. According to the decreasing scale of MVMCA after induction of GA, patients were classified into two groups: the NORMAL group (n = 521) if MVMCA decreased <30% and the LOW group (n = 399) if MVMCA decreased ⩾30%.

After CEA, TCD examinations were performed 2 to 6 hours postoperatively at the bedside. If MVMCA were higher than 200% of the baseline value or patients had any clinical symptom of CHS, TCD would be repeated at the discretion of physicians and further confirmed by CT or MR (Fig. 2).

Surgical procedure:

All patients underwent the operation under GA induced with sufentanyl or fentanil. During the operation, the blood pressure was maintained at the patient's high normal range during clamping. After the operation, the systolic blood pressure (SBP) and diastolic blood pressure (DBP) were carefully controlled less than 140

mmHg and 90 mmHg respectively for at least five days according to the local clinical protocol.

Trained neurosurgeons performed all CEAs under an intraoperative microscope (OPMI Pentero®, Germany) with the standard surgical procedure. Selective shunting was performed depending on whether MVMCA decreased ⩾50% of the baseline after carotid cross-clamping by TCD monitoring. The external carotid artery and common carotid artery were de-clamped before the internal carotid artery releasing in order to remove residual emboli. At the end of the CEA, the artery was sutured without patch.

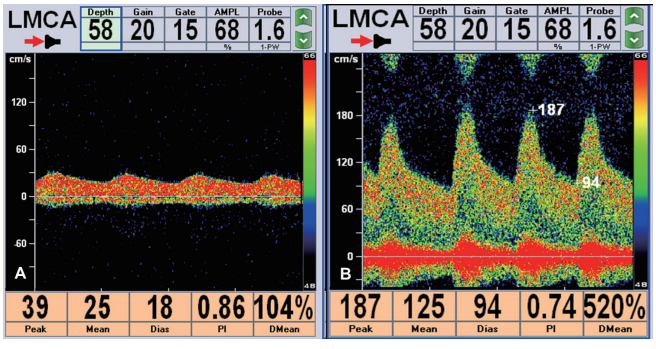

Figure 1 (A) Transcranial color Doppler (TCD) demonstrated decreased blood flow in the left MCA (the affected side) after general anesthesia. The peak velocity was 38 cm/s, the diastolic velocity was 21cm/s, the mean velocity was 27 cm/s, and the PI was 0.62. (B) After carotid artery de-clamping, the TCD showed higher blood flow on the left/affected side. The peak velocity was 187 cm/s, the diastolic velocity was 94 cm/s, the mean velocity was 125 cm/s, and the PI was 0.74. The delta mean percentage was 520% as compared to the value at the baseline.

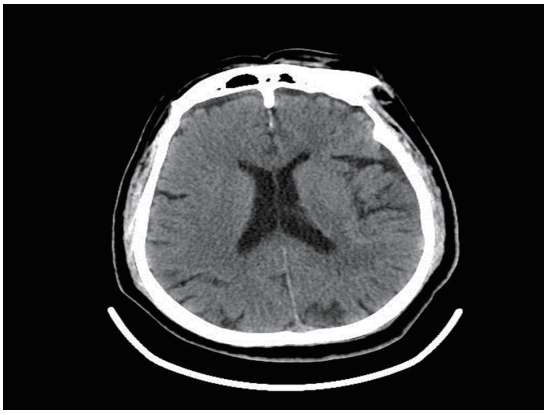

Figure 2 After given the diagnosis of hyperperfusion per TCD criteria, the CT scan was performed. The result was negative. There were no symptoms for the patient.

Statistical analysis

The Chi-square test was used to compare the differences of categorical variables, such as, the risk factors of atherosclerosis, symptomatic or asymptomatic, and degree of stenosis before CEA. Student's t-test was used to see if the variable is continuous one (including the blood flow velocities, MAP, HR and PCO_2 during the operation). To identify predictors of decrease in cerebral flow, a logistic regression with backward was approached. $P < 0.05$ was considered statistically significant. SPSS (Version 21.0, IBM, USA) was used for the statistical analysis.

Results

Patients' clinico-demographic characteristics

Nine-hundred twenty patients with completed TCD data were included in the final analysis. The age ranges from 32 to 84 years, and 108 (11.7%) are females. There were 52 (5.7%) patients with moderate stenosis (50% - 69%) and 868 (94.3%) patients with severe stenosis (70% - 99%). No significant difference was observed in the vascular risk factors, such as hypertension, coronary heart disease, hyperlipidemia, and smoking, between the NORMAL and LOW groups except the status of diabetes (Table 1). The presence of anterior communicating artery (ACoA) and posterior communicating artery (PCoA) was significantly higher in NORMAL group (60.1% vs 39.9%, $P = 0.01$). There was no significant difference between the two groups (47.4% vs 52.6%, $P = 0.15$) in the number of patients with ipsilateral MCA lesion.

Parameters comparison between two groups

At the baseline after GA, the values of PSV, EDV, and MV of MCA were lower in the LOW group but they increased significantly higher than the NORMAL group within 5 minutes after de-clamping. However, there was no significant difference in patients with MAP or PCO_2 both at the baseline and after de-clamping. Lower HR was showed in the LOW group at both phases (Table 2).

Cerebral blood flow, hyperperfusion and CHS

The occurrence of CHS per ultrasonographic criteria was higher in the LOW group (21.3% vs 15.7%, $P = 0.03$), but was similar per clinical CHS criteria between the two groups (3.2% vs 2.1%, $P = 0.28$). There was no significant difference of perioperative cerebral infarcts between the LOW and NOMAL groups (5.8% vs 5.0%, $P = 0.60$) (Table 3).

Factors associated with decrease in flow velocity

Under the logistic regression analysis, diabetic status (OR = 1.35, 95%CI: 1.01~1.79, $P = 0.04$) and decreasing HR (OR = 0.98, 95%CI: 0.97~0.99, $P < 0.05$) were predictive of decreased flow velocity after GA. The presence of ACoA/PCoA collateral circulations was a protective factor of maintaining stable blood flow after GA (OR = 0.75, 95%CI: 0.57~0.98, $P = 0.03$). No significant difference was observed in the degree of vascular stenosis (Table 4).

Table 1 Patients' Clinico-demographic Characteristics

Variable	All patients *n* = 920	NORMAL group *n* = 521	LOW group *n* = 399	*P*
Age	63 ± 8	63 ± 7	62 ± 8	0.24
Female	108(11.7)	57(10.9)	51(12.8)	0.39
Hypertension	652(70.9)	363(69.7)	289(72.4)	0.36
Diabetes	279(30.3)	144(27.6)	135(33.8)	0.04
CHD	203(22.1)	106(20.3)	97(24.3)	0.15
Hyperlipidemia	328(35.7)	183(35.1)	145(36.3)	0.70
Smoking	608(66.1)	352(67.6)	256(64.2)	0.28
TIA/Stroke	779(84.7)	442(84.8)	337(84.5)	0.88
Ipsilateral MCA Lesion	57(6.2)	27(5.2)	30(7.5)	0.15
Contralateral Occlusion	37(4.0)	25(4.8)	12(3.0)	0.18
ICA >70% Stenosis	868(94.3)	499(9.6)	369(9.2)	0.03
ACoA/PCoA	524(57.0)	315(60.1)	209(52.4)	0.01
Shunt	150(16.3)	79(15.2)	71(17.8)	0.28

CHD, coronary heart disease; ACoA, anterior communicate artery; PCoA, posterior communicate artery; MCA, middle cerebral artery; ICA, internal carotid artery

Table 2 Cerebral Blood Flow Velocities and Anesthesia Parameters during CEA

Parameters	NORMAL group (*n* = 521)	LOW group (*n* = 399)	*P*
MAP baseline (mmHg)	93 ± 9	93 ± 10	0.79
HR baseline (beat/min)	65 ± 11	63 ± 10	<0.05
PCO_2 baseline (mmHg)	34 ± 3	34 ± 4	0.15
MVMCA baseline (cm/s)	47 ± 15	36 ± 13	<0.01
PIMCA baseline	0.82 ± 0.20	0.89 ± 0.21	<0.01
MAP de-clamping (mmHg)	91 ± 12	92 ± 12	0.21
HR de-clamping (beat/min)	69 ± 12	66 ± 11	<0.01
PCO_2 de-clamping (mmHg)	35 ± 5	34 ± 3	0.20
MVMCA de-clamping (cm/s)	70 ± 27	58 ± 25	<0.01
PIMCA de-clamping	1.03 ± 0.21	1.04 ± 0.20	0.43
Increasing Delta MVMCA (%)	153 ± 54	164 ± 69	0.01

MAP, mean artery pressure; HR, heart rate; PCO_2, pressure of carbon dioxide; MCA, middle cerebral artery; MV, mean velocity; PI, pulsatility index

Table 3 Occurrence of Hyperperfusion, CHS and Perioperative Cerebral Infarcts

Variable	Total *n* = 920 (%)	NORMAL group *n* = 521 (%)	LOW group *n* = 399 (%)	*P*
Hyperperfusion (TCD criteria)	167 (18.2)	82 (15.7)	85 (21.3)	0.03
CHS (clinical criteria)	24 (2.6)	11 (2.1)	13 (3.2)	0.28
PCI	49 (5.3)	26 (5.0)	23 (5.8)	0.60

CHS, cerebral hyperperfusion syndrome; TCD, transcranial Doppler; PCI, perioperative cerebral infarct

Table 4 Risk Factors Associated with Decrease in Flow Velocity after GA

Risk factors	Beta	OR	95% CI	*P*
Diabetes	0.30	1.35	1.01-1.79	0.04
ACoA/PCoA	−0.29	0.75	0.57-0.98	0.03
HR	−0.02	0.98	0.97-0.99	<0.01

ACoA, anterior communicative artery; PCoA, posterior communicative artery; HR, heart rate; OR, odds ratio; CI, confidence interval

Discussion

The present study demonstrates that the decrease of blood flow velocities after GA is not associated with CHS or cerebral infarct perioperative. Although occurrence of hyperperfusion per ultrasonographic criteria was significantly higher in the LOW group; similar proportion of patients in both groups develop clinical CHS. Diabetes and decreasing in heart rate associated with GA are risk factors of decrease in flow velocities while having ACoA/PCoA collateral is a protecting factor. Overall, GA did not put patient at risk for CHS as well as periopeative cerebral infarcts.

Impaired dynamic cerebral autoregulation has been reported in patients with severe (> or =70%) ICA stenosis [9]. After GA, the blood flow of MCA decreases accordingly as BP drops and HR slows down. The magnitude of decreasing in flow velocity is influenced by the dynamic cerebral autoregulation. It has been demonstrated that the velocity of MCA has a positive correlation with the level of brain metabolism [10], and it can be affected by several factors [8]. Although BP fluctuates within a certain range; the cerebral blood flow remains stable which is known as the autoregulation of cerebral blood flow [11]. Maintaining stable BP is a critical step for a successful operation. In this study, all patients maintained stable BP intraoperatively, and their BP were managed strictly as systolic BP below 140 mmHg for 5 days after surgery [12].

If patients have concomitant ipsilateral severe stenosis or occlusion of MCA, the cerebral blood flow would further drop. Intracranial stenosis or occlusion is associated with poor perioperative neurological outcome. The previous study showed that patients with intracranial lesions benefit less from endarterectomy during one-year follow-up period [13]. Other study demonstrated that patients with and without carotid tandem lesion who underwent CEA had similar rates of stroke and death [14-15]. Ballotta et al.[14] analyzed 1,143 patients who underwent CEA. Their results showed no significant perioperative ipsilateral strokes difference between those patients with (0.9 %) and without (0.5 %) carotid tandem lesion (P = 0.62). The 5-year ipsilateral stroke-free, any stroke-free, and overall survival rates did not differ significantly. In our study, there was also no difference between groups with or without MCA lesions.

Research from Beckman et al. showed that diabetes mellitus is an independent risk factor for the atherothrombotic cardiovascular disease. Adults with diabetes are two to four times more likely to develop heart disease or stroke than adults without diabetes [16]. It is well known that as a result of diabetes mellitus, the small-vessel disease may impair autoregulation which becomes one of the main risk factors of CHS [2]. In our study, diabetes was also shown to be an influencing factor of cerebral blood flow decrease after GA. Significant lowing was observed in the LOW group which means impaired autoregulation but not attribute to CHS directly yet. Also, HR changes have a certain effect on cerebral perfusion and autoregulation. Reduction of HR in cardiac output would lead to cerebral hypoperfusion and velocity decreasing of MCA accordingly [17]. In this study, it was showed lower HR in the LOW group.

In severe carotid artery stenosis or occlusion, intracranial collateral is a central compensational mechanism. TCD can evaluate the presence of communication arteries by detecting the change of the blood flow direction and the blood flow velocity [18]. The activated ACoA/PCoA compensation in occluded carotid disease is critical to ensure the autoregulation [19]. Poor collateral flow and diminished cerebrovascular reactivity or reserves are potential risk factors for CHS [2]. In this study, we found that presence of collateral circulation is a protected factor for stabilization of cerebral blood flow after GA.

Although most patients with CHS have mild symptoms and signs at the beginning, rapid progression to severe and even life-threatening condition can occur if CHS is not recognized and treated early [2]. The incidence of CHS was reported to be as high as 10% if patients met “hyperperfusion” per TCD criteria [20]. In this cohort, the occurrence of ultrasonographical hyperperfusion was higher in general (21.3% vs 15.7%), but the development of clinical CHS is relatively low (3.2% vs 2.1%). Newman et al.[6] found that an increase of >100% in mean MCA velocity at 1 and 10-min post-clamp release have a positive predictive values (PPV) of 1.2% and 20.0% of CHS, respectively. They failed to demonstrate that significant increases in MCA velocity were predictive of postoperative CHS.

Complications of CEA also include the incidence of stroke caused by ischemia especially during carotid artery clamping. The decreasing of blood flow after GA may lead to lower blood supply after carotid clamping. In this study, the occurrence of perioperative cerebral infarcts was not significant different between the two groups (5.0% vs 5.8%). Therefore, decreased flow

velocities after GA are not associated with CHS or perioperative cerebral infarction. For these patients, the index of MCA velocity intra-operative increasing >100% as a predictor of CHS is needed to be further explored. The ratio is increasing or combining with other values may improve the prediction sensitivity and specificity of CHS.

The main limitation of our study came from its single-center with retrospective study design, and certain bias cannot be completely ruled out. In addition, although anesthetics and temperature may affect the cerebral blood flow velocity, all patients were treated with sufentanyl or remifentanil and took surgery in the constant temperature operation room, quantitative analysis is needed for further study. Finally, the operator variability of intraoperative monitoring may affect the measurement of blood velocity.

Conclusions

In summary, decreased cerebral flow velocities after GA are not associated with CHS or perioperative cerebral infarction while diabetes is a risk factor of cerebral blood flow decreases. The presence of ACoA/PCoA is a protective factor for the stability of cerebral blood flow after GA.

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Conflict of Interest

The authors have no conflict of interest to declare.

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