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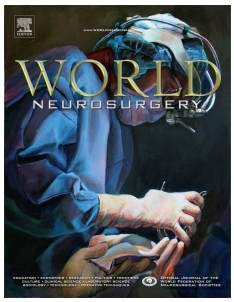

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Impaired dynamic cerebral autoregulation as a predictor for cerebral hyperperfusion after carotid endarterectomy: A prospective observational study

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Running title: Predictive utility of dCA for CH after CEA

Keywords： Carotid endarterectomy, cerebral autoregulation, cerebral hyperperfusion, hemodynamics, Transcranial Doppler Ultrasound

Impaired dynamic cerebral autoregulation as a predictor for cerebral hyperperfusion after carotid endarterectomy: A prospective observational study

Abstract

Objective: Cerebral hyperperfusion syndrome (CHS) is a severe complication of carotid endarterectomy (CEA). Because cerebral hyperperfusion (CH) reduces the benefits of CEA, it is important to identify patients at high risk of developing CH. We investigated dynamic cerebral autoregulation (dCA) as a potential predictor of CH after CEA.

Methods: In a prospective observational study of 90 patients, we defined CH as a ≥ 100% increase in the transcranial Doppler ultrasound-derived mean flow velocity of the middle cerebral artery compared to baseline, with or without clinical manifestations. We examined dCA in the supine position and during squat-stand maneuvers using the transfer function, analyzing phase, gain, and coherence. Logistic regression analysis and receiver operating characteristic curves were used to assess the relationships between variables and outcomes.

Results: CH occurred in 18 patients after CEA. The CH group had a lower ipsilateral phase for both body postures than the non-CH group at very low and low frequencies, respectively (both $P < 0.01$). Postoperative CH was independently associated with the preoperative peak systolic velocity $(PSV)_{sten}/PSV_{dis}$ ratio and the ipsilateral phase in both body postures at a very low frequency. Receiver operating characteristic curve analysis showed that the ipsilateral phase had excellent CH predictive accuracy in the supine position and squat-stand maneuvers at a very low frequency (areas under the curve: 0.809 and 0.839, respectively, both $P < 0.001$; cutoff values: 24.7 and 11.7, respectively).

Conclusions: The lower ipsilateral phase may serve as a predictor of CH after CEA.

Keywords: Carotid endarterectomy, Cerebral autoregulation, Cerebral hyperperfusion, Hemodynamics, Transcranial Doppler Ultrasound

Introduction

Atherosclerotic stenosis of the carotid artery is a major cause of ischemic stroke. Carotid endarterectomy (CEA) is considered the standard treatment for reducing the risk of stroke in patients with severe carotid stenosis. Cerebral hyperperfusion (CH) is defined as an excessive increase in ipsilateral cerebral blood flow (CBF) relative to metabolic needs following carotid revascularization.[1]

Cerebral hyperperfusion syndrome (CHS) is a rare but important perioperative complication of CEA. It is characterized by an ipsilateral headache, eye and face pain, vomiting, seizures, focal neurological deficits, and intracranial hemorrhage (ICH).[1-3] Although the reported incidence of CHS is 1%–3%, the morbidity and mortality rates among patients with CHS who present with ICH are as high as 50%.[1,4] CHS often occurs in patients with CH.[5] Given that CHS reduces the benefits of CEA, especially among patients with asymptomatic carotid disease, it is important to identify patients at a high risk of developing CHS.

Impaired cerebrovascular autoregulation is crucially involved in CH.[2] Dynamic cerebral autoregulation (dCA) refers to the ability to adapt cerebral vasoconstriction and vasodilation according to blood pressure (BP) fluctuations within a certain range to regulate and stabilize CBF.[6] As the brain is highly dependent on the continuous supply of oxygenated blood, reduced effectiveness of dCA increases the brain's sensitivity to hypoperfusion and hyperperfusion.[7] Transfer function analysis (TFA), the most widely used dCA monitoring

method, has been employed to study ischemic stroke, ICH, and neurodegeneration, among other diseases.[8-10] However, few studies have used TFA to investigate CEA.

Ultrasound combined with transcranial Doppler ultrasound (TCD) provides information regarding hemodynamics and dCA. TCD is a reliable tool to identify post-reperfusion hyperperfusion and correlates with perfusion magnetic resonance (MR) imaging.[11] Moreover, preoperative hemodynamics and dCA may be useful imaging markers for clinically predicting CHS. Therefore, this study investigated the utility of impaired dCA as a potential predictor of CH after CEA.

Methods

Research participants

This study was approved by the Ethics Committee of the Capital Medical University Xuanwu Hospital (approval number [2019]073). All experimental procedures were performed following the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

We prospectively included 90 consecutive patients who underwent CEA at Xuanwu Hospital, Capital Medical University, China, between March 2021 and September 2022. The inclusion criteria were as follows: (1) Severe (70–99%) unilateral carotid artery stenosis diagnosed by duplex ultrasound and confirmed by computed tomography angiography (CTA) or digital subtraction angiography (DSA) based on the criteria used in the North American Symptomatic Carotid Endarterectomy Trial,[12] and (2) age of 18–80 years. The exclusion criteria were as follows: (1) CEA performed for non-atherosclerotic diseases; (2) severe stenosis (70%–99%) or occlusion of the contralateral carotid artery, bilateral subclavian artery, and/or vertebrobasilar artery; (3) moderate or higher-grade stenosis of the unilateral or bilateral middle cerebral artery (MCA); (4) hybrid operation or unsuccessful carotid

revascularization; (5) poor temporal window prohibitive of TCD monitoring; and (6) heart failure, congenital heart disease, severe cardiac arrhythmia, acute or chronic infection, or other serious systemic diseases. Figure 1 represents a flow chart of patient enrollment.

Carotid artery ultrasound and transcranial color code sonography

All patients underwent preoperative duplex ultrasound evaluation of the carotid artery and MCA by sufficiently trained doctors with > 5 years of experience in vascular ultrasound. This assessment was performed using a Hitachi Ascendus (Hitachi, Inc., Tokyo, Japan) ultrasound instrument with a 4.0–8.0 MHz micro curvilinear transducer, 2.0–5.0 MHz convey array probes, and 1.0–5.0 MHz phased array probes. While measuring carotid velocity, the angle between the ultrasound beam and blood flow was set to ≤ 60°. The MCA velocity was measured at < 30°. All acquired images were stored in a picture archiving and communication system for subsequent analyses.

The imaging parameters were as follows: (1) peak systolic velocity (PSV_{sten}) and end diastolic velocity (EDV_{sten}) at the carotid stenosis; (2) peak systolic velocity (PSV_{dis}) and end diastolic velocity (EDV_{dis}) at 4–6 cm beyond the carotid bifurcation; and (3) PSV, diastolic velocity, and pulsatility index (PI) of the ipsilateral (PIoper) and contralesional (PIcon) MCA before CEA. Subsequently, we calculated the ratios PSV_{sten}/PSV_{dis} and PIcon/PIoper.

Study protocol/dCA measurement

All dCA data were collected in an environmentally controlled laboratory (22°C–24°C) with non-sensory stimuli (e.g., noise, lights) controlled based on the international white paper of cerebral autoregulation assessments.[7] Participants were asked to refrain from nicotine, caffeine, chocolate, and alcohol consumption for at least 12 h and high calorie meals for at least 4 h before the study. Furthermore, participants were asked to refrain from moderate-

vigorous exercise for at least 6 h prior to measurement. After lying down at rest for 15 min with uncrossed legs, the examination was started.

Participants were fitted with a head frame. Continuous cerebral blood flow velocity (CBFV) was measured in the bilateral MCA at a depth of 50–65 mm through the temporal window with 1.6 MHz ultrasound probes using TCD (EMS-9D Pro; Delica Medical, Shenzhen, China). We recorded non-invasive continuous beat-to-beat BP (NIBP) using a servo-controlled plethysmograph (Finometer; Enschede, Netherlands) attached to the finger. Before each NIBP measurement, brachial BP was measured using a sphygmomanometer (Omron HBP-1300; Kyoto, Japan) to calibrate the baseline BP signal. The sampling frequency of the Doppler trace and NIBP signal was 125 Hz.[13] The heart rate was measured via four-lead electrocardiography. Respiratory rate and end-tidal carbon dioxide (Et-CO_2) during spontaneous breathing were recorded using a nasal cannula with a nasal capnograph.

Baseline. Once satisfactory signals were obtained from all equipment, we obtained the baseline brachial BP, heart rate, and Et-CO_2 measurements within a 10-min period with the participants in the supine position while breathing room air.

Squat-stand maneuvers (SSMs). After standing for 2 min, the participants performed a maximum of 15 SSMs at a 0.05-Hz frequency (standing for 10 s, squatting for 10 s). The squats involved bending the knees at 45° for 10 s, followed by standing straight for another 10 s.[14] A voice prompt provided by a computer program was used to ensure that the SSMs were performed at the standard frequency. A highchair was placed in front of the participants, which they could lightly touch to maintain balance if required. A bed was set at the correct height behind the participants to guide the depth of each squat; moreover, participants were instructed not to place any weight on the bed.[15] Throughout each recording, the participants

were asked to breathe through their noses and avoid Valsalva-like maneuvers during the SSMs. Verbal communication was avoided during data collection. After the SSMs, the participants were placed in the supine position for 2 min (Figure 2).

dCA analysis

Cerebral autoregulation parameters were calculated based on TFA,[7] with NIBP and CBFV as the input and output signals, respectively. TFA is based on the Fourier decomposition of stationary input and output signals into the sums of sines and cosines of multiple frequencies. The transfer function estimates of the dCA metrics were calculated at very low frequency (VLF, 0.02–0.07 Hz), low frequency (LF, 0.07–0.20 Hz), and high frequency (HF, 0.20–0.50 Hz), with gain, phase, and coherence parameters.[16] This phase shift represented the time delay of the CBFV response to NIBP. The gain represented the damping effect of dCA on the magnitude of BP oscillations. Coherence helped to identify conditions in which estimates of gain and phase may be unreliable. We only estimated dCA parameters if the coherence was > 0.5.

CEA

CEA was performed under general anesthesia, with all patients administered the same anesthetic regimen. All CEA procedures were performed by experienced vascular surgeons. Conventional CEA was performed as previously described.[17] Throughout the operation, patients were monitored using TCD (EMS-9PB, Delica, Shenzhen, China) and routine electrocardiographic monitoring. CH was defined as an intraoperative increase in the TCD-derived mean flow velocity in the middle cerebral artery ($MCAV_{mean}$) by ≥ 100% after carotid de-clamping compared with baseline $MCAV_{mean}$ from de-clamping to suturing, regardless of clinical manifestations. CHS was defined as CH combined with clinical symptoms such as

headache, confusion, seizures, ICH, or focal neurological deficits, following a symptom-free interval.[18]

Other clinical and imaging characteristics

We collected patients' demographic and clinical data, including age, sex, height, and weight; neurological and cardiovascular history; and vascular risk factors, including hypertension, diabetes mellitus, dyslipidemia, smoking history, and alcohol consumption. In case the anterior communicating artery and/or posterior communicating artery were visible on computed tomography angiography or MR angiography, this was defined as the "presence of primary collaterals." Additionally, we recorded the patients' clinical symptoms and preoperative and postoperative brain MR imaging findings.

Statistical analysis

Statistical analyses were performed using SPSS Statistical Software 22.0 (IBM Corporation, Armonk, NY, USA) and MedCalc version 19.6.1 (MedCalc Software, Ostend, Belgium). All continuous variables were tested for normal distribution using the Shapiro–Wilk test, with normally and non-normally distributed variables expressed as mean ± standard deviation and median (interquartile range), respectively. Categorical variables are presented as n (%). Between-group comparisons of normally and non-normally variables were performed using the independent Student t-test or Mann–Whitney U-test, respectively. The chi-square test was used for between-group comparisons of categorical variables. Multivariate analysis was conducted using a logistic regression model, including factors with $P < 0.10$ in the univariate analysis. Receiver operating characteristic (ROC) curve analysis was performed to identify the cutoff value. The area under the curve (AUC), optimal cutoff value, sensitivity, and specificity were calculated. ROC curves were compared using

DeLong's test. A two-sided $P < 0.05$ was considered statistically significant and confidence intervals (CIs) were set at 95%.

Results

Characteristics of the study population

We included 90 patients in the study (82 men and 8 women; mean age: 63.1 ± 7.6 years [range, 37–80 years]). CEA was successfully performed in all patients. Table 1 presents the baseline demographic characteristics, clinical data, and laboratory test results of the CH (n = 18) and non-CH (n = 72) groups. There were no significant between-group differences regarding demographics, vascular risk factors, or laboratory indices. Regarding hemodynamic parameters, the PSV_{sten}/PSV_{dis} was higher in the CH group than in the non-CH group ($P < 0.001$).

dCA parameters in the CH and non-CH groups in the supine position and during SSMs

Table 2 and Table 3 show the dCA values in both groups during the supine position and SSMs. The CH group had a lower ipsilateral phase degree than the non-CH group during the supine position and SSMs in both the VLF and LF ranges (all $P < 0.01$) but not in the HF range. Additionally, there were no significant differences in the gain and absolute gain between the supine position and SSMs ($P > 0.05$). Squat-stand maneuvers showed higher coherence than supine maneuvers in all patients in the very low and low frequency range (all $P < 0.001$); however, there was no significant difference in the high frequency range ($P = 0.904$).

Multivariate analysis

PSV_{sten}/PSV_{dis} (adjusted odds ratio [aOR]: 1.114, 95% CI: 1.029–1.206, $P = 0.008$),

ipsilateral phase (supine) at the VLF (aOR: 0.938, 95% CI: 0.894–0.985, $P = 0.01$), and ipsilateral phase (SSMs) at the VLF (aOR: 0.929, 95% CI: 0.877–0.985, $P = 0.013$) were identified as independent predictors of CH after CEA.

Comparison of ROC curves

We compared the ROC curves of four models. Model 1 comprised only the ipsilateral phase (supine) at the VLF; Model 2 comprised the ipsilateral phase (SSMs) at the VLF; Model 3 comprised a combination of Model 1 with the PSV_{sten}/PSV_{dis} ratio; Model 4 comprised a combination of Model 2 and PSV_{sten}/PSV_{dis} ratio. For Models 1, 2, 3, and 4, the AUCs were 0.809 (95% CI: 0.712–0.884), 0.839 (95% CI: 0.746–0.908), 0.883 (95% CI: 0.799–0.942), and 0.869 (95% CI: 0.781–0.931), respectively, with no significant between-model differences ($P = 0.119$ for Model 1 vs. Model 3; $P = 0.272$ for Model 2 vs. Model 4) (Figure 3). The optimal cutoff phase value used to distinguish patients with and without CH was obtained based on the maximum Youden index. The optimal cutoff values of the ipsilateral phase (supine) and ipsilateral phase (SSMs) at the VLF for predicting CH were ≤ 24.7 and ≤ 11.7, respectively. The proportion of patients with CH in the ipsilateral phase (supine) ≤ 24.7 group was significantly higher than that in the ipsilateral phase (supine) > 24.7 group (50.0% vs. 5.0%, $P < 0.001$). Furthermore, the proportion of patients with CH in the ipsilateral phase (SSMs) ≤ 11.7 group was significantly higher than that in the ipsilateral phase (SSMs) > 11.7 group (68.4% vs. 7.0%, $P < 0.001$) (Figure 4).

Discussion

This single-center prospective study explored the relationship of hemodynamic or dCA parameters of CH after CEA in patients with carotid stenosis. We found that higher PSV_{sten}/PSV_{dis} ratios and lower ipsilateral phase degrees were strongly associated with CH

after CEA. Moreover, the ipsilateral phase (supine) and ipsilateral phase (SSMs) in the VLF showed high predictive utility for CH after CEA, which did not increase with the inclusion of the PSV_{sten}/PSV_{dis} ratio. This finding demonstrates the predictive utility of dCA for CH after CEA, with high sensitivity and specificity.

Impaired cerebral autoregulation is the most widely accepted mechanism contributing to the development of CHS.[1] Chronic severe carotid stenosis leads to chronic brain ischemia. The arterioles and capillaries of patients with dysfunctional cerebral autoregulation are more vulnerable to rupture and bleeding upon an abrupt increase in perfusion pressure following revascularization.[2] We used TFA to analyze the dCA. The phase degree (supine) in both the VLF and LF ranges was lower in the CH group than in the non-CH group. This result suggests that patients with CH have more severely impaired dCA than patients without CH. Furthermore, we compared differences in the dCA during the supine position and SSMs. The phases in the VLF and LF ranges were markedly lower in the CH group than in the non-CH group. Regarding SSMs, the large oscillations in evoked BP were transmitted to cerebral perfusion, which increased the coherence between these variables and optimizes the TFA method and its reproducibility. Consistent with previous studies,[14,19] we observed increased coherence in both groups during SSMs compared with the supine position in the VLF and LF ranges. This high coherence is usually indicative of the reliability of the assessed dCA indices. Additionally, the benefit of an additional dCA measurement during SSMs was found, which increased the specificity (91.67% vs. 79.17%). This could facilitate the identification of patients at risk of CH. However, there were no significance between-group differences in gain and absolute gain. One explanation for this may be that the phase is determined from the time delay between BP and CBF, and hence, is insensitive to any amplitude scaling.[20] Moreover, the phase is less sensitive to missing data than the gain and is reportedly a more reliable measure of dCA in clinical studies.[21-23] Another explanation may be that we included

a high proportion of patients with asymptomatic carotid artery stenosis, in whom dCA was not severely impaired.

Previous studies have investigated the predictive utility of changes in the PSV of the MCA on the surgical side at de-clamping,[5] postoperative increase ratio of the MCA[24], and velocity BP index[25] for CHS. We focused on extracranial carotid hemodynamics and found that the PSV_{sten}/PSV_{dis} ratio was an independent predictor of CH, attributable to the negative association between the PSV ratio and cerebral perfusion. Previous research indicated that higher of PSV_{sten}/PSV_{dis} ratios are associated with severe stenosis[26,27]. Several recent studies have confirmed that severe carotid artery stenosis is a risk factor for CHS.[2,28,29]One study found a significantly higher incidence of hyperperfusion-induced intracranial hemorrhage after carotid artery stenting in patients with near-total occlusion than in those without (10.1% vs 0%).[28] Patients with severe unilateral carotid stenosis (⩾90%) have a higher risk of hyperperfusion-induced intracranial hemorrhage after carotid artery stenting than those with less severe stenosis. According to Fan et al., the CH risk in patients with near-total occlusion had a 6.3-fold higher than that in patients with less severe stenosis. [29] The PSV ratio offers a more accurate and steadier parameter than arterial flow velocity measurement, which is affected by the presence of hypertension, hypotension, cardiac insufficiency, anemia, hyperthyroidism, and other diseases.[30] However, the presence of calcified atherosclerotic plaques and near-total occlusions may affect the prediction accuracy.[31]

Regarding the frequency domain of the dCA, we chose a VLF range of SSMs (0.02–0.07 Hz), considered to reflect the most relevant real-time dynamic dCA behavior.[32] The PSV_{sten}/PSV_{dis} and phase degree of the MCA reflect extracranial hemodynamic and cerebral autoregulation. Both parameters are safe, cost-effective, and easy to use. Herein, the incidence of CHS after CEA was 2.2%; further, 11.1% of patients with CH developed CHS.

Prediction seeks to improve prompt interventions, which help prevent adverse events.

Accordingly, BP was more strictly controlled in patients at high risk for CHS. This might have reduced the occurrence of CHS and underestimated the positive predictive value of our index. In the present study, the addition of preoperative hemodynamic parameters did not improve the predictive value of dCA for CH after CEA. However, given the small number of patients with CHS, further studies on the mechanism underlying CHS are warranted.

This study has some limitations. First, this was a single-center study conducted in a university hospital setting, with a small sample size given the low incidence of CHS. Therefore, large-scale prospective studies in different settings are warranted to validate our findings. Second, we enrolled more men than women. Stroke and carotid artery stenosis are more common in men than in women[33]; moreover, there is a higher proportion of women with a poor temporal window than men. Third, TCD can only measure the velocity, not the flow volume. However, an MR angiography study reported that the MCA diameter did not significantly change in response to arterial pressure and CO_2 changes.[34,35] Therefore, the measured velocity is equivalent to the flow volume.

Conclusions

This study identified the lower ipsilateral phase as a predictor of CH after CEA. Impaired dCA may serve as a novel predictive tool for identifying patients who are at high risk of developing CH after CEA.

List of Abbreviations

aOR, adjusted odds ratio; AUC, area under the curve; BP, blood pressure; CBF, cerebral blood flow; CBFV, cerebral blood flow velocity; CEA, carotid endarterectomy; CH, cerebral hyperperfusion; CHS, cerebral hyperperfusion syndrome; CI, confidence interval; dCA, dynamic cerebral autoregulation; EDV, end diastolic velocity; Et-CO_2, end-tidal carbon

dioxide; HF, high frequency; ICH, intracranial hemorrhage; LF, low frequency; MCA, middle cerebral artery; $MCAV_{mea}$, mean flow velocity in the middle cerebral artery; NIBP, non-invasive continuous beat-to-beat BP; PI, pulsatility index; PIcon, contralesional; PIoper, ipsilateral; PSV, peak systolic velocity; ROC, receiver operating characteristic; SSM, squat-stand maneuver; TCD, transcranial Doppler ultrasound; TFA, transfer function analysis; VLF, very low frequency

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References

1. van Mook WN, Rennenberg RJ, Schurink GW, et al. Cerebral hyperperfusion syndrome. *Lancet Neurol*. 2005;4:877-888. https://doi.org/10.1016/S1474-4422(05)70251-9.

2. Lin YH, Liu HM. Update on cerebral hyperperfusion syndrome. *J Neurointerv Surg*. 2020;12:788-793. https://doi.org/10.1136/neurintsurg-2019-015621.

3. Kirchoff-Torres KF, Bakradze E. Cerebral hyperperfusion syndrome after carotid

revascularization and acute ischemic stroke. *Curr Pain Headache Rep*. 2018;22:24. https://doi.org/10.1007/s11916-018-0678-4.

4. Ogasawara K, Sakai N, Kuroiwa T, et al. Intracranial hemorrhage associated with cerebral hyperperfusion syndrome following carotid endarterectomy and carotid artery stenting: retrospective review of 4494 patients. *J Neurosurg*. 2007;107:1130-1136. https://doi.org/10.3171/JNS-07/12/1130.

5. Dalman JE, Beenakkers IC, Moll FL, Leusink JA, Ackerstaff RG. Transcranial doppler monitoring during carotid endarterectomy helps to identify patients at risk of postoperative hyperperfusion. *Eur J Vasc Endovasc Surg*. 1999;18:222-227. https://doi.org/10.1053/ejvs.1999.0846.

6. Xiong L, Liu X, Shang T, et al. Impaired cerebral autoregulation: measurement and application to stroke. *J Neurol Neurosurg Psychiatry*. 2017;88:520-531. https://doi.org/10.1136/jnnp-2016-314385.

7. Claassen JA, Meel-van den Abeelen AS, Simpson DM, Panerai RB, international Cerebral Autoregulation Research Network (CARNet). Transfer function analysis of dynamic cerebral autoregulation: a white paper from the international cerebral autoregulation research network. *J Cereb Blood Flow Metab*. 2016;36:665-680. https://doi.org/10.1177/0271678X15626425.

8. Xiong L, Tian G, Lin W, et al. Is dynamic cerebral autoregulation bilaterally impaired after unilateral acute ischemic stroke? *J Stroke Cerebrovasc Dis*. 2017;26:1081-1087. https://doi.org/10.1016/j.jstrokecerebrovasdis.2016.12.024.

9. Oeinck M, Neunhoeffer F, Buttler KJ, et al. Dynamic cerebral autoregulation in acute intracerebral hemorrhage. *Stroke*. 2013;44:2722-2728. https://doi.org/10.1161/STROKEAHA.113.001913.

10. Indelicato E, Fanciulli A, Poewe W, Antonini A, Pontieri FE, Wenning GK. Cerebral

349 autoregulation and white matter lesions in Parkinson's disease and multiple system
350 atrophy. *Parkinsonism Relat Disord*. 2015;21:1393-1397.
351 https://doi.org/10.1016/j.parkreldis.2015.10.018.
352 11. Kneihsl M, Hinteregger N, Nistl O, et al. Post-reperfusion hyperperfusion after
353 endovascular stroke treatment: a prospective comparative study of TCD versus MRI.
354 *J NeuroIntervent Surg*. 2022; neurintsurg-2022-019213. https://doi.org/10.1136/jnis-
355 2022-019213.
356 12. Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients
357 with symptomatic moderate or severe stenosis. North American Symptomatic Carotid
358 Endarterectomy Trial Collaborators. *N Engl J Med*. 1998;339:1415-1425.
359 https://doi.org/10.1056/NEJM199811123392002.
360 13. Zhang R, Zuckerman JH, Iwasaki K, Wilson TE, Crandall CG, Levine BD. Autonomic
361 neural control of dynamic cerebral autoregulation in humans. *Circulation*.
362 2002;106:1814-1820. https://doi.org/10.1161/01.cir.0000031798.07790.fe.
363 14. Junejo RT, Braz ID, Lucas SJ, et al. Neurovascular coupling and cerebral autoregulation
364 in atrial fibrillation. *J Cereb Blood Flow Metab*. 2020;40:1647-1657.
365 https://doi.org/10.1177/0271678X19870770.
366 15. Batterham AP, Panerai RB, Robinson TG, Haunton VJ. Does depth of squat-stand
367 maneuver affect estimates of dynamic cerebral autoregulation? *Physiol Rep*.
368 2020;8:e14549. https://doi.org/10.14814/phy2.14549.
369 16. Zhang R, Zuckerman JH, Giller CA, Levine BD. Transfer function analysis of dynamic
370 cerebral autoregulation in humans. *Am J Physiol*. 1998;274:H233-H241.
371 https://doi.org/10.1152/ajpheart.1998.274.1.h233.
372 17. Chen Y, Song G, Jiao L, Wang Y, Ma Y, Ling F. A study of carotid endarterectomy in a
373 Chinese population: initial experience at a single center. *Clin Neurol Neurosurg*.

2014;126:88-92. https://doi.org/10.1016/j.clineuro.2014.08.025.

18. Fassaert LMM, Immink RV, van Vriesland DJ, et al. Transcranial doppler 24 hours after carotid endarterectomy accurately identifies patients not at risk of cerebral hyperperfusion syndrome. *Eur J Vasc Endovasc Surg*. 2019;58:320-327. https://doi.org/10.1016/j.ejvs.2019.04.033.

19. Claassen JA, Levine BD, Zhang R. Dynamic cerebral autoregulation during repeated squat-stand maneuvers. *J Appl Physiol (1985)*. 2009;106:153-160. https://doi.org/10.1152/japplphysiol.90822.2008.

20. Panerai RB, Brassard P, Burma JS, Castro P, Claassen JA, van Lieshout JJ, et al. Transfer function analysis of dynamic cerebral autoregulation: a CARNet white paper 2022 update. J Cereb Blood Flow Metab. 2023; 43:3-25.

21. Deegan BM, Serrador JM, Nakagawa K, Jones E, Sorond FA, Olaighin G. The effect of blood pressure calibrations and transcranial doppler signal loss on transfer function estimates of cerebral autoregulation. *Med Eng Phys*. 2011;33:553-562. https://doi.org/10.1016/j.medengphy.2010.12.007.

22. Intharakham K, Beishon L, Panerai RB, Haunton VJ, Robinson TG. Assessment of cerebral autoregulation in stroke: a systematic review and meta-analysis of studies at rest. *J Cereb Blood Flow Metab*. 2019;39:2105-2116. https://doi.org/10.1177/0271678X19871013.

23. Sheriff F, Castro P, Kozberg M, et al. Dynamic cerebral autoregulation post endovascular thrombectomy in acute ischemic stroke. *Brain Sci*. 2020;10:641. https://doi.org/10.3390/brainsci10090641.

24. Li QP, Hua Y, Liu JB, et al. Intraoperative transcranial Doppler monitoring predicts the risk of cerebral hyperperfusion syndrome after carotid endarterectomy. World Neurosurg. 2022;165:e571-e580. https://doi.org/10.1016/j.wneu.2022.06.100.

399 25. Lai ZC, Liu B, Chen Y, Ni L, Liu CW. Prediction of cerebral hyperperfusion syndrome
400 with velocity blood pressure index. *Chin Med J (Engl)*. 2015;128:1611-1617.
401 https://doi.org/10.4103/0366-6999.158317.
402 26. Soulez G, Therasse E, Robillard P, et al. The value of internal carotid systolic velocity
403 ratio for assessing carotid artery stenosis with Doppler sonography. *AJR Am J*
404 *Roentgenol*. 1999;Jan;172:207-212. https://doi.org/10.2214/ajr.172.1.9888769.
405 27. Ranke C, Creutzig A, Becker H, Trappe HJ. Standardization of carotid ultrasound: a
406 hemodynamic method to normalize for interindividual and interequipment variability.
407 *Stroke*. 1999;Feb;30:402-406. https://doi.org/10.1161/01.str.30.2.402.
408 28. Zhang L, Dai D, Li Z, et al. Risk factors for hyperperfusion-induced intracranial
409 hemorrhage after carotid artery stenting in patients with symptomatic severe carotid
410 stenosis evaluation. *J Neurointerv Surg*. 2019;11:474-478.
411 https://doi.org/10.1136/neurintsurg-2018-013998.
412 29. Fan X, Lai Z, Lin T, et al. Multidelay MR arterial spin labeling perfusion map for the
413 prediction of cerebral hyperperfusion after carotid endarterectomy. *J Magn Reson*
414 *Imaging.* 2023;58:1245-1255. https://doi.org/10.1002/jmri.28634.
415 30. The Professional Committee of Vascular Ultrasound of Stroke Prevention and Treatment
416 Expert, Committee of the National Health Commission, The Professional Committee
417 of Superficial Organ and Peripheral Vascular Ultrasound of the Chinese Medical
418 Ultrasound Engineering, The Professional Committee of Craniocerebral and Cervical
419 Vascular Ultrasound of the Chinese Medical Ultrasound Engineering. Expert
420 consensus on some issues of cerebral and carotid vascular ultrasonography. *Adv*
421 *Ultrasound Diagn Ther*. 2021;02:153-162.
422 https://doi.org/10.37015/AUDT.2021.200057.
423 31. Brouwers JJWM, Jiang JFY, Feld RT, et al. A New Doppler-Derived Parameter to

Quantify Internal Carotid Artery Stenosis: Maximal Systolic Acceleration. *Ann Vasc Surg*. 2022; 81:202-210. https://doi.org/10.1016/j.avsg.2021.09.056.

32. Haubrich C, Wendt A, Diehl RR, Klötzsch C. Dynamic autoregulation testing in the posterior cerebral artery. *Stroke*. 2004;35:848-852. https://doi.org/10.1161/01.STR.0000120729.99039.B6.

33. Bonati LH, Jansen O, de Borst GJ, Brown MM. Management of atherosclerotic extracranial carotid artery stenosis. *Lancet Neurol*. 2022;21:273-283. https://doi.org/10.1016/S1474-4422(21)00359-8.

34. Serrador JM, Picot PA, Rutt BK, Shoemaker JK, Bondar RL. MRI measures of middle cerebral artery diameter in conscious humans during simulated orthostasis. *Stroke*. 2000;31:1672-1678. https://doi.org/10.1161/01.str.31.7.1672.

35. Verbree J, Bronzwaer AS, Ghariq E, et al. Assessment of middle cerebral artery diameter during hypocapnia and hypercapnia in humans using ultra-high-field MRI. *J Appl Physiol (1985)*. 2014;117:1084-1089. https://doi.org/10.1152/japplphysiol.00651.2014.

Figure legends

Figure 1 Flowchart of patient enrollment

Figure 2 The study protocol.

All the enrolled patients received dCA measurement before carotid endarterectomy. The dCA measurement included supine position (10 min), standing (2 min), and squat-stand maneuvers (5 min).

448 **Figure 3** Between-model comparisons of ROC curves for predicting the outcome.

449 Model 1: the ipsilateral phase (supine) at very low frequency, *dark purple line*. Model 2: the

450 ipsilateral phase (SSMs) at very low frequency, *green line*. Model 3: Model 1 +

451 PSV_{sten}/PSV_{dis}, *orange line*. Model 4: Model 2 + PSV_{sten}/PSV_{dis}, *green dotted line*.

452 PSV, peak systolic velocity; ROC, receiver operating characteristics; SSMs, squat-stand

453 maneuvers

454

455 **Figure 4** Number of patients according to different cut-off values of ipsilateral phase.

456 **(**a) The proportion of patients with CH in the ipsilateral phase (supine) ≤ 24.7 group was

457 significantly higher than that in the ipsilateral phase (supine) > 24.7 group (50.0% vs. 5.0%,

458 $P < 0.001$). (b) The proportion of patients with CH in the ipsilateral phase (SSMs) ≤ 11.7

459 group was significantly higher than that in the ipsilateral phase (SSMs) > 11.7 group (68.4%

460 vs. 7.0%, $P < 0.001$)

461 CH, cerebral hyperperfusion; SSMs, squat-stand maneuvers

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Table 1. Clinical characteristics and hemodynamic parameters.

Characteristic	All(n=90)	CH(n=18)	Non-CH(n=72)	*P*
Demographic variables				
Age,years	63.1±7.6	61.8±6.6	63.5±7.8	0.395
Male	82(91.1)	15(83.3)	67(93.1)	0.195
BMI	25.0±2.7	24.7±2.6	25.0±2.7	0.643
Vascular risk factors				
Hypertension	61(67.8)	15(83.3)	46(63.9)	0.160
Diabetes mellitus	34(37.8)	8(44.4)	26(36.1)	0.514
hyperlipidemia	46(51.1)	10(55.6)	36(50.0)	0.673
coronary artery disease	19(21.1)	3(16.7)	16(22.2)	0.754
smoking	66(73.3)	14(77.8)	52(72.2)	0.771
alcohol	48(53.3)	10(55.6)	38(52.8)	0.833
Laboratory indexes				
Serum triglycerides, mmol/L	1.3(0.9-1.6)	1.3(0.9-1.8)	1.3(0.9-1.6)	0.646
Total cholesterol, mmol/L	3.4(3.0-4.1)	3.2(2.9-3.6)	3.5(3.1-4.2)	0.195
High-density lipoprotein, mmol/L	1.0(0.8-1.1)	0.9(0.8-1.1)	1.0(0.8-1.2)	0.293
Low-density lipoprotein, mmol/L	1.9(1.5-2.4)	1.7(1.5-2.1)	1.9(1.5-2.5)	0.385
Hemodynamic parameters				
PSV_{sten}/ PSV_{dis}	7.9(5.7-14.1)	17.3(12.3-32.3)	7.1(5.4-11.0)	< 0.001
PIcon/PIoper	1.4(1.2-1.5)	1.5(1.2-1.6)	1.3(1.2-1.5)	0.092
Presence of primary collaterals	79(87.8)	14(77.8)	65(90.3)	0.220

Operation side, right	51(56.7)	13(72.2)	38(52.8)	0.136
Post-operative imaging				
asymptomatic acute embolic lesions	9(10)	1(5.6)	8(11.1)	0.102
hemorrhagic complications	1(11.1)	1(5.6)	0	

BMI: body mass index; PSV_{sten}/PSV_{dis}: ratio of peak systolic velocity at the carotid stenosis to peak systolic velocity at 4–6 cm beyond the carotid bifurcation; PIcon/PIoper: ratio of the pulsatility index of the ipsilateral middle cerebral artery to the pulsatility index of the contralesional middle cerebral artery; Presence of primary collaterals: anterior communicating artery and/or posterior communicating artery appearing on computed tomography angiography or magnetic resonance angiography images.

Table 2. Cerebral autoregulation parameters before endarterectomy during the supine position.

Frequency	Parameters	CH(n=18)	Non-CH(n=72)	*P*
VLF	phase (degree)			
	ipsilateral	**18.29(8.34-24.57)**	**42.12(30.16-55.91)**	**< 0.001**
	contralateral	47.01(27.17-65.97)	51.15(40.01-69.41)	0.242
	gain [cm/ (s·mm Hg)]			
	ipsilateral	0.60(0.46-0.93)	0.64(0.48-0.84)	0.844
	contralateral	0.71(0.57-0.93)	0.73(0.61-0.97)	0.657
	gain (%/mm Hg)			

	ipsilateral	1.04(0.76-1.33)	1.04(0.85-1.29)	0.996
	contralateral	1.01(0.73-1.21)	1.10(0.87-1.38)	0.071
	coherence			
	ipsilateral	0.80(0.75-0.87)	0.69(0.64-0.74)	< 0.001
	contralateral	0.70(0.65-0.78)	0.67(0.64-0.73)	0.157
LF	phase (degree)			
	ipsilateral	**13.31(4.50-24.20)**	**31.45(17.12-42.08)**	**0.001**
	contralateral	25.96(14.87-43.53)	37.98(27.73-51.31)	0.076
	gain [cm/ (s·mm Hg)]			
	ipsilateral	0.57(0.39-0.83)	0.68(0.56-0.86)	0.131
	contralateral	0.80(0.67-0.91)	0.91(0.66-1.09)	0.299
	gain (%/mm Hg)			
	ipsilateral	0.97(0.75-1.22)	1.15(0.92-1.51)	0.056
	contralateral	1.15(0.95-1.32)	1.28(1.03-1.65)	0.074
	coherence			
	ipsilateral	0.72(0.68-0.77)	0.68(0.64-0.76)	0.327
	contralateral	0.70(0.64-0.74)	0.70(0.64-0.74)	0.801
HF	phase (degree)			
	ipsilateral	27.97(8.20-47-37)	20.15(12.18-29.20)	0.105
	contralateral	22.28(12.20-35.45)	19.40(10.13-28.26)	0.276
	gain [cm/ (s·mm Hg)]			
	ipsilateral	0.54(0.38-0.73)	0.61(0.45-0.82)	0.250

	contralateral	0.69(0.60-0.94)	0.81(0.67-1.06)	0.119
	gain (%/mm Hg)			
	ipsilateral	0.89(0.61-1.19)	1.04(0.78-1.35)	0.153
	contralateral	1.03(0.92-1.25)	1.17(1.00-1.44)	0.069
	coherence			
	ipsilateral	0.76(0.71-0.79)	0.74(0.69-0.79)	0.697
	contralateral	0.74(0.68-0.78)	0.75(0.70-0.79)	0.374
Et-CO_2		38.1±2.1	38.5±2.0	0.395

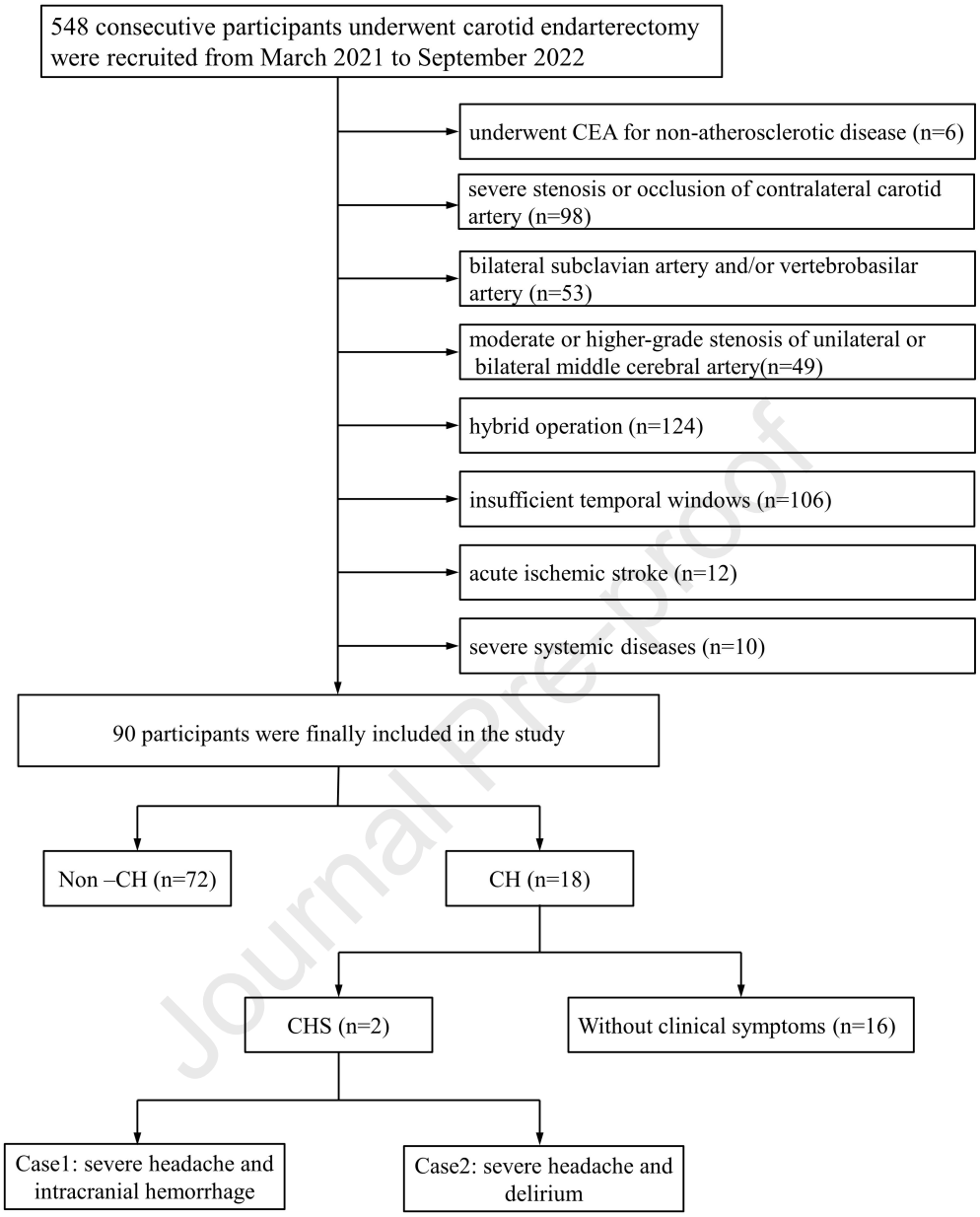
VLF: very low frequency; LF: low frequency; HF: high frequency; Et-CO_2: end-tidal carbon dioxide.

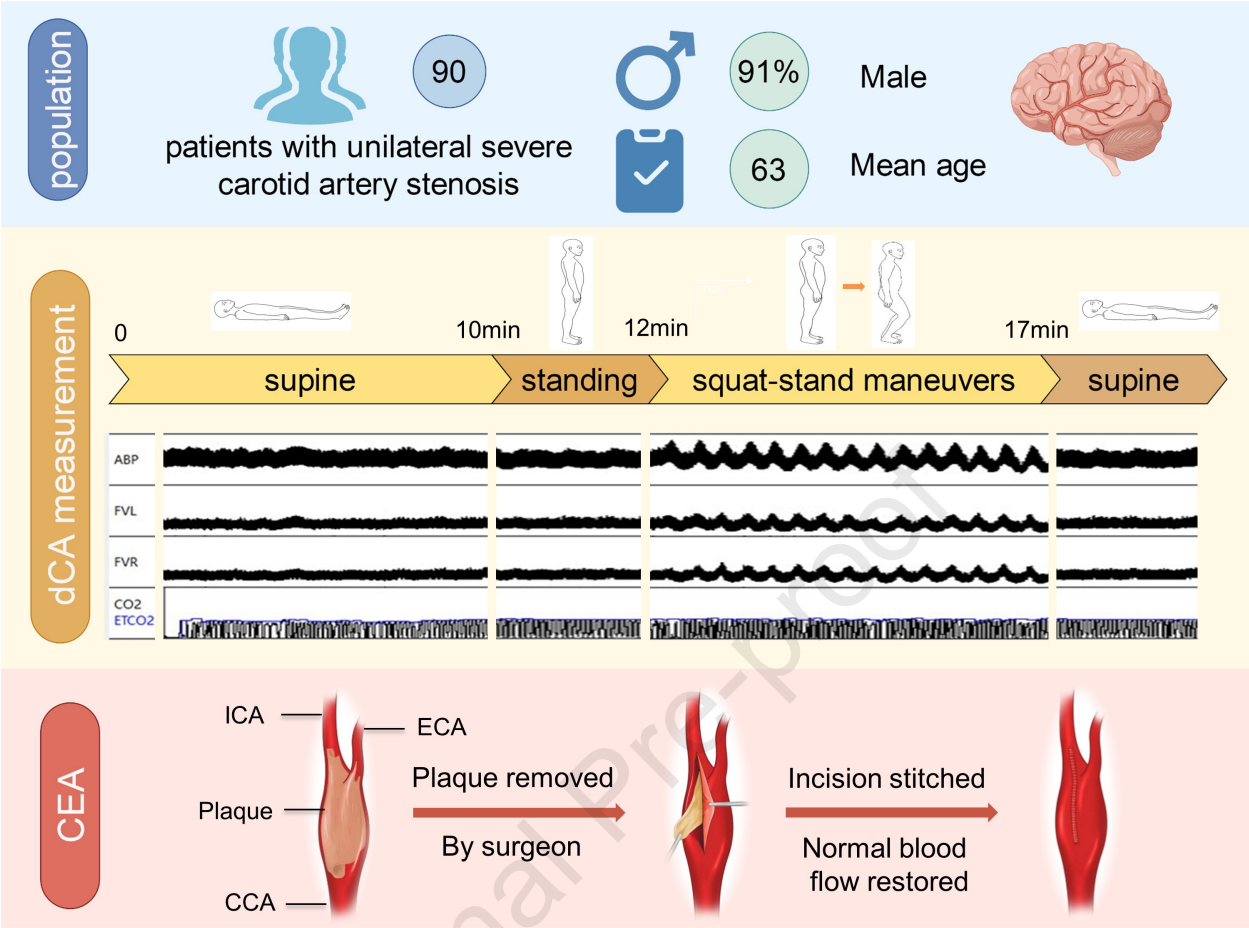
Table 3. Cerebral autoregulation parameters before endarterectomy during squat-stand maneuvers.

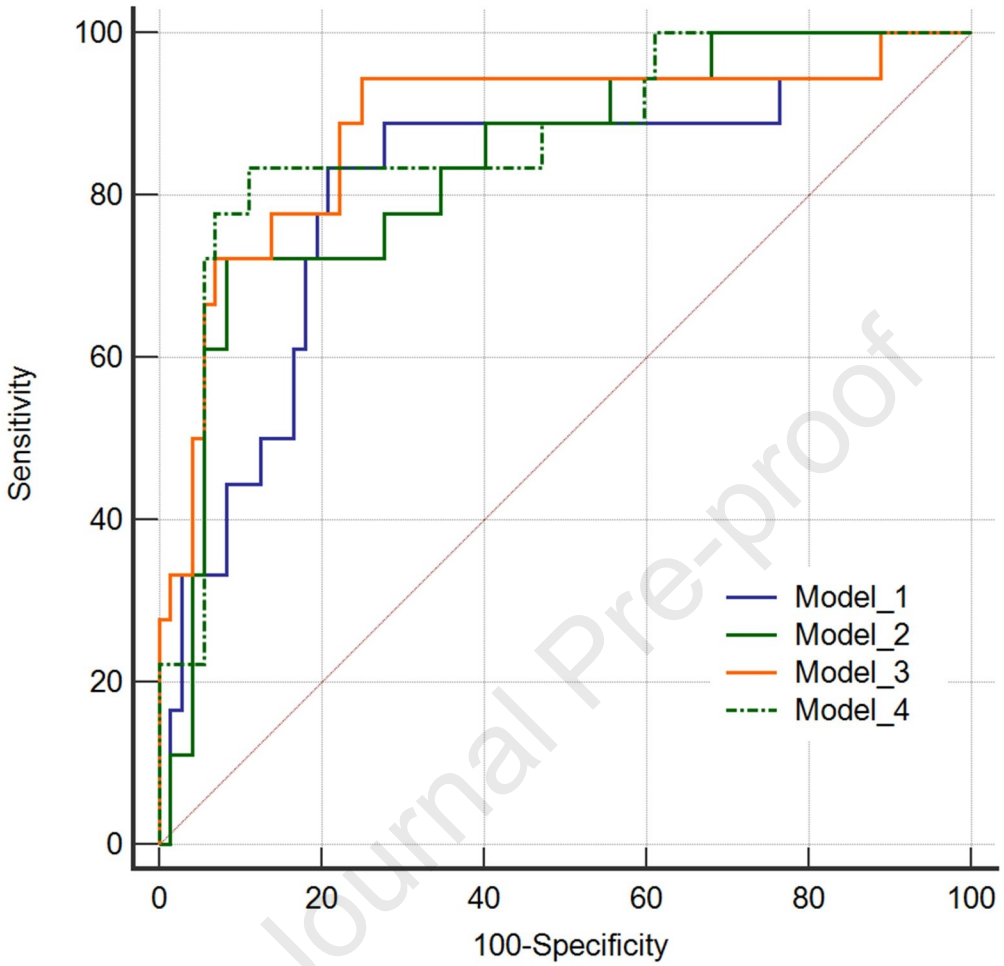
Frequency	Parameters	CH(n=18)	Non-CH(n=72)	*P*
VLF	phase (degree)			
	ipsilateral	**9.36(6.39-25.25)**	**34.04(23.14-51.27)**	**< 0.001**
	contralateral	49.32(32.31-65.07)	46.13(36.31-58.06)	0.840
	gain [cm/ (s·mm Hg)]			
	ipsilateral	0.65(0.41-0.74)	0.59(0.50-0.81)	0.690
	contralateral	0.68(0.54-0.89)	0.70(0.56-0.97)	0.900
	gain (%/mm Hg)			
	ipsilateral	1.09(0.97-1.35)	1.13(0.96-1.47)	0.657
	contralateral	0.98(0.89-1.16)	1.13(0.91-1.46)	0.105
	coherence			
	ipsilateral	0.93(0.88-0.95)	0.91(0.86-0.94)	0.223
	contralateral	0.89(0.75-0.91)	0.91(0.87-0.94)	0.056
LF	phase (degree)			

	ipsilateral	**7.69(4.04-20.55)**	**22.12(14.07-29.49)**	**0.001**
	contralateral	23.88(16.85-40.59)	29.49(20.60-40.45)	0.455
	gain [cm/ (s·mm Hg)]			
	ipsilateral	0.61(0.43-0.83)	0.77(0.56-0.91)	0.095
	contralateral	0.84(0.70-1.21)	0.97(0.76-1.21)	0.372
	gain (%/mm Hg)			
	ipsilateral	1.08(0.79-1.36)	1.28(1.03-1.65)	0.119
	contralateral	1.20(0.97-1.47)	1.41(1.13-1.64)	0.063
	coherence			
	ipsilateral	0.79(0.72-0.81)	0.78(0.72-0.84)	0.720
	contralateral	0.74(0.66-0.83)	0.78(0.73-0.83)	0.248
HF	phase (degree)			
	ipsilateral	22.96(11.67-28.74)	16.18(9.16-21.64)	0.146
	contralateral	17.78(7.27-22.10)	17.53(12.26-25.75)	0.545
	gain [cm/ (s·mm Hg)]			
	ipsilateral	0.58(0.39-0.79)	0.65(0.53-0.79)	0.323
	contralateral	0.86(0.58-1.33)	0.90(0.66-1.14)	0.880
	gain (%/mm Hg)			
	ipsilateral	1.09(0.67-1.26)	1.21(0.98-1.41)	0.386
	contralateral	1.20(0.91-1.50)	1.31(1.12-1.77)	0.101
	coherence			
	ipsilateral	0.74(0.68-0.77)	0.74(0.67-0.80)	0.603
	contralateral	0.75(0.66-0.78)	0.75(0.68-0.82)	0.470
Et-CO_2		38.6±1.9	38.2±2.0	0.494

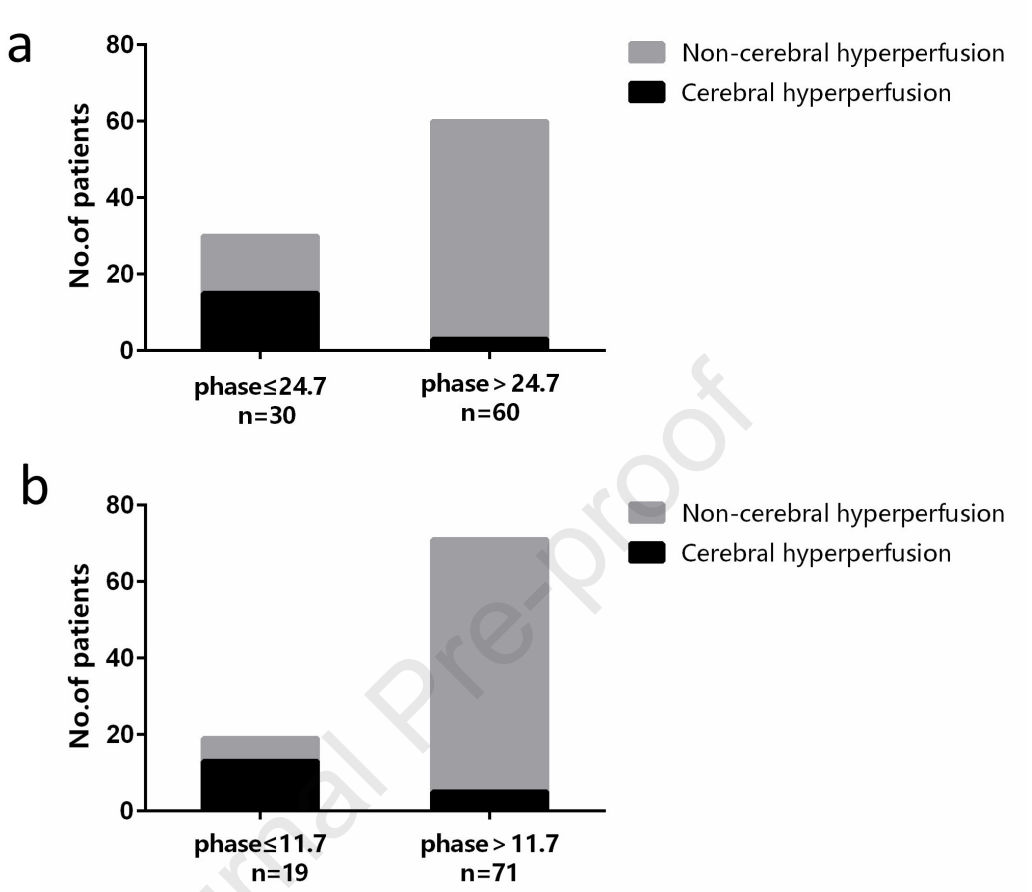
VLF: very low frequency; LF: low frequency; HF: high frequency; Et-CO_2: end-tidal carbon dioxide.







	AUC	95%CI	sensitivity	specificity
Model 1	0.809	0.712-0.884	83.33%	79.17%
Model 2	0.839	0.746-0.908	72.22%	91.67%
Model 3	0.883	0.799-0.942	94.44%	75.0%
Model 4	0.869	0.781-0.931	83.33%	88.89%



List of Abbreviations

aOR, adjusted odds ratio; AUC, area under the curve; BP, blood pressure; CBF, cerebral blood flow; CBFV, cerebral blood flow velocity; CEA, carotid endarterectomy; CH, cerebral hyperperfusion; CHS, cerebral hyperperfusion syndrome; CI, confidence interval; dCA, dynamic cerebral autoregulation; EDV, end diastolic velocity; Et-CO_2, end-tidal carbon dioxide; HF, high frequency; ICH, intracranial hemorrhage; LF, low frequency; MCA, middle cerebral artery; $MCAV_{mea}$, mean flow velocity in the middle cerebral artery; NIBP, non-invasive continuous beat-to-beat BP; PI, pulsatility index; PIcon, contralesional; PIoper, ipsilateral; PSV, peak systolic velocity; ROC, receiver operating characteristic; SSM, squat-stand maneuver; TCD, transcranial Doppler ultrasound; TFA, transfer function analysis; VLF, very low frequency

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Na Li: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft. **Fubo Zhou**: Data curation, Formal analysis, Writing – review & editing. **Xia Lu**: Data curation, Writing – review & editing. **Hongxiu Chen:** Data curation, Methodology, Writing – review & editing. **Ran Liu**: Data curation, Methodology, Writing – review & editing. **Songwei Chen**: Data curation, Methodology, Writing – review & editing. **Yingqi Xing:** Project administration, Investigation, Methodology, Writing – review & editing.