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*Original Article*

# Combination of transcranial Doppler and end-tidal carbon dioxide partial pressure in evaluating cerebrovascular reserve of patients with intracranial angiostegnosis

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**Abstract:** The study aims to apply the combination of transcranial Doppler (TCD) and end-tidal carbon dioxide partial pressure ($ETCO_2$) for evaluating the cerebrovascular reserve (CVR) in the patients with intracranial angiostegnosis. 42 CVR patients, who were confirmed by TCD and (or) digital subtraction arteriography (DSA) as the unilateral or bilateral middle cerebral artery stenosis and (or) combined with other intracranial, exterior main artery stenosis, were collected. Another 30 cases were set as the control group. The included patients were monitored $ETCO_2$ by TCD and QL software. The methods of inhaling the autologous $CO_2$ gas, as well as the hyperventilation, were used to measure CVR by inducing the hypercapnia and hypocapnia, respectively. We found that the expansion reserve of the severer side in the multiple vascular stenosis group was significantly lower than the normal group ($P<0.05$). The overall CVR of the severer side in the multiple vascular stenosis group was significantly lower than the diseased side in the lateral artery stenosis group ($P<0.05$). The vascular lesion degrees were negatively correlated with the vasodilator reserve values and the overall reserve values of the severer side ($P<0.05$). The more severe the intracranial angiostegnosis, the worse CVR. In conclusion, the combination of TCD and $ETCO_2$ could be effectively used in the evaluation and research of CVR.

**Keywords:** Transcranial Doppler, cerebrovascular reserve, angiostegnosis, end-tidal carbon dioxide partial pressure, digital subtraction arteriography

## Introduction

The cerebrovascular disease is a major disease that would hazard the human health, the cerebrovascular reserve (CVR) is the body's endogenous ability of anti-ischemia [1], referring to the cerebrovascular abilities that could maintain the normal and stable cerebral blood flow through the autoregulation under the physiological or pathological state, including the brain structural reserve, cerebral blood flow reserve, brain functional reserve and brain metabolism reserve. Its dysfunction has an important role in the ischemic cerebrovascular diseases, and is the independent risk factor for the ischemic stroke [2, 3]. The effective CVR monitoring would have the important clinical significance towards the prediction, prevention and prognosis of ischemic stroke [4]. Therefore, there existed the broad prospects towards the CVR study [5].

Currently, the commonly used CVR-evaluation imaging techniques included the positron emission tomography, single photon emission computed tomography (SPECT) [6], Xe-CT [7], CT perfusion imaging and magnetic resonance imaging, laser Doppler, transcranial ultrasound harmonic perfusion imaging and near infrared spectral analysis, etc [8, 9]. The positron emission tomography was the gold standard in quantitatively evaluating the abilities of blood vessels' dilation, but this method had the shortcomings as complex equipment, expensive price and radioactive hazards, etc, making it difficult to spread. As a non-invasive ultrasound, the transcranial Doppler ultrasound (TCD) could detect the local blood flow velocity and direction of intracranial artery [10, 11], thus indirectly reflecting the cerebral blood flow and evaluating CVR, because it was simple, non-invasive, low cost, repeatable, etc., it had been widely used in the clinical practice. The research of combining TCD and vasodilatation provocation test to evaluate CVR had been carried out for a long period, and the commonly used methods included the $CO_2$ inhalation [12], intravenous injection of acetazolamide, breath test and increasing the physiological dead space to produce the hypercapnia, thus inducing the cerebrovascular expansion, the above methods could detect the changes of perfusion parameters between the initial perfusion and post-vasodilation stimulus perfusion under the basic state, thus evaluating cerebrovasodilation reserve. And through the cerebral vasoconstriction caused by the hyperventilation-resulted hypocapnia, the cerebral vasoconstriction reserve could also be evaluated. There had been some reports about the cardiovascular side effects caused by the $CO_2$ inhalation and intravenous injection of acetazolamide-induced hypercapnia, the acetazolamide injection might induce the dizziness, mild headache and feeling sluggish [13], while the long-time $CO_2$ inhalation might easily cause the patient's discomfort.

In this study, the combination of TCD and end-tidal carbon dioxide partial pressure ($ETCO_2$) was used to evaluate CVR of the patients with intracranial vascular lesions and the healthy populations, the autologous $CO_2$ gas inhalation method was used to induce the hypercapnia, and the hyperventilation method was used to induce the hypocapnia, aiming to evaluate the CVR method towards the patients with the intracranial vascular disease and healthy people, which had the repeatability, and compared with the hypercapnia induced by the $CO_2$ inhalation and intravenous injection of acetazolamide, it was quick, easy, non-invasive and well tolerated, and the cost was low, thus it had the extensive research space and clinical application values.

## Materials and methods

### *Subjects*

The case group included a total of 42 cases, treated for the ischemic cerebrovascular diseases in our department from May 2008 to April 2009, including 29 males and 13 females, age range: 39 to 80 years old, with the mean age as (59.31±10.61 years old). ① Confirmed as the unilateral or bilateral MCA stenosis by DSA or TCD examination, or combined with other intracranial, exterior main artery stenosis, met the TCD ultrasound diagnostic criteria of cerebral vascular stenosis [14]. ② The bilateral temporal windows had the good acoustic window, which could show a clear flow spectrum. ③ Because the experiment required the patients to cooperate highly, thus the patients should have the clear consciousness, and were able to complete the actions according to instructions. ④ No serious cardiopulmonary disease. ⑤ Age range: 39-80 years old. The normal control group: 30 healthy people were selected from our hospital, including 16 males and 14 females, age range: 29-74 years old, with the mean age as 54.5±11.1 years old, having no heart or cerebrovascular diseases, and were all excluded from the history of hypertension and diabetes. The two-sample t test revealed that the case group and the control group had t = 1.848, Sig (2-tailed) = 0.069, $P>0.05$, there had no significant difference in the age between the 2 groups, and this experiment was comparable. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Baotou Central Hospital. Written informed consent was obtained from all participants.

### *Inspection method of CVR*

Multi-Dop*4 transcranial Doppler ultrasound detector (DWL, Germany) and QL software (Compumedics Germany GmbH, Germany), with the bilateral-probe frequency as 2MHz, was used to monitor the blood flow velocities of bilateral middle cerebral arteries, and the head frame was used for the fixation, the external $CO_2$ device was used to monitor the $CO_2$ partial pressure at the end stage of expiration. 1) Quiet breathing: this test was conducted at 16:00-21:00, all the enrolled patients were in the supine position, and the $CO_2$ test mode was on the Doppler instrument, when the patient was in the calm breathing, an ordinary single lumen oxygen tube was connected to the $CO_2$ monitoring equipment to monitor $ETCO_2$, after obtaining the bilateral MCA Doppler spectrum, the head frame was fixed for another 4-5 min monitoring. 2) Hypocapnia induction: the patient was told to perform the hyperventilation, deeply breathing with the fastest speed for about 30-60 s to induce the hypocapnia, then maintained 4-5 min when the flow rate and $ETCO_2$ restored to the basic state. 3) Hypercapnia induction: the ordinary oxygen mask, with one 2-m gas pipe, was buckled onto the patient's face, so that the patient would inhale his/her exhaled $CO_2$ to induce the hypercapnia, the changes of $ETCO_2$ and blood flow velocity were then observed for 30-60 s, when the blood flow velocity and $ETCO_2$ were stable and exhibited no further increase, the mask was removed. 4) Analysis: during the whole process, the subject would be urged the nose breathing. When the blood flow velocity and $ETCO_2$ returned to the normal, the window was frozen, and the results were stored in the hard disk for the offline analysis. The measurement parameters included the blood flow velocities and $ETCO_2$ of bilateral MCA in the calm and hyperventilation status, as well as during the the autologous $CO_2$ inhalaiton. The clinical trials had been approved by the Ethics Committee of Baotou Central Hospital, and the enrolled subjects all signed the informed consent.

*Calculation*

$$CVRI = \frac{|V_{after\ change} - V_{baseline}|}{V_{baseline}} \times 100\% \div \left| ETCO_{2after\ change} - ETCO_{2baseline} \right|$$

This formula was the more commonly used CVR calculation method. And the result was called as the CVR index (CVRI), the result of this formula was the relative slope, referring to the change percentage of corresponding blood flow velocity per mmHg $CO_2$ partial pressure change, the cerebrovascular $CO_2$ reactivity was expressed by the change percentage of middle cerebral artery blood flow speed to the every mmhg change of end-expiratory $CO_2$ partial pressure in the exhaled gases ($ETCO_2$) and the $CO_2$ partial pressure in the artery (Pa, $CO_2$), which could much more objectively describe the change extents of cerebral blood flow velocity to the $CO_2$ partial pressure, and divided into the vasodilator reserve, the vasoconstriction reserve and the overall reserve. Because of the invasion caused by directly monitoring the arterial blood gas partial pressures ($PaCO_2$, $PaO_2$, etc.), as well as the $CO_2$ partial pressure of carotid blood ($PjvCO_2$), it was not generally accepted by the normal people. Therefore, when applying TCD to evaluate CVR, the infrared $CO_2$ gas analyzer was normally used to monitor the $CO_2$ partial pressure in the end-expiratory exhaled gas to replace the arterial $CO_2$ partial pressure.

*Statistical analysis*

All the data were expressed as mean ± standard deviation ($\bar{x}\pm s$), and processed with the SPSS13.0 software package, the data of each group were performed the normality test and homogeneity of variance test, the average data were performed the independent sample t test and ANOVA, partial indicators were performed the Spearman rank correlation analysis. $\alpha$ = 0.05 was set as the standard test towards all the measurement data, with $P<0.05$ considered as the statistical significance.

## Results

*42 patients of the case group*

A total of 42 patients of the case group were confirmed as the unilateral or bilateral MCA stenosis by the TCD examination, TCD conventional examination, or DSA; and combined with other intracranial and exterior main artery stenosis: among who 10 patients exhibited the left middle cerebral artery (LMCA) stenosis: seven cases were mild, two cases were moderate and 1 case was severe. 8 patients exhibited the right middle cerebral artery (RMCA) stenosis: 7 cases were mild and 1 case was moderate.

12 cases exhibited two or more intra- or extracranial stenosis: two cases were mild bilateral MCA stenosis, 1 case was severe, and 9 cases exhibited that the LMCA or RMCA stenosis was combined with other intracranial vascular stenosis. 12 cases exhibited the combination of at least one vessel occlusion: 1 case of LMCA occlusion; 1 case of RMCA occlusion; 1 case of LICA occlusion; 1 case of RICA occlusion; 1 case of bilateral ICA occlusion; 1 case of bilateral ICA severe occlusion, accompanied with left vertebral arterial occlusion; 4 cases of unilateral MCA stenosis accompanied with other vascular occlusion; 2 cases of other intracranial vascular occlusion.

*Grouping of the case group according to the vascular lesion degrees*

The unilateral MCA stenosis group: the left or right middle cerebral artery stenosis. According to the location of vascular lesion, the diseased

**Table 1.** CVR of both sides based on the lesion severity ($\overline{x}\pm s$, %/mmHg)

| Group | Cases | | Constriction reserve | Dilation reserve | Overall reserve |
|---|---|---|---|---|---|
| Normal control | 30 | L | 3.27±0.95 | 3.54±1.66 | 3.19±0.81 |
| | | R | 3.06±0.86 | 3.81±1.63 | 3.23±0.70 |
| Lateral MCA stenosis | 18 | Diseased side | 3.26±2.37 | 3.65±2.62 | 3.22±1.27 |
| | | Healthy side | 3.35±1.83 | 3.68±1.86 | 3.24±1.26 |
| Multiple vascular stenosis | 24 | Severer side | 2.60±1.78 | 1.99±2.78[a] | 2.30±1.14[b,c] |
| | | Lighter side | 3.06±1.93 | 2.99±2.15 | 2.84±1.02 |

Note: a compared with the normal control group, $P<0.05$ b compared with the normal control group $P<0.01$, c compared with the lateral middle cerebral artery stenosis group, $P<0.01$.

**Table 2.** Mean, maximum, minimum, and standard deviation of end-respiratory $CO_2$ of the case group and the normal group

| Group | Cases | Calm breathing $ETCO_2$ (mmhg) | Low $CO_2$ $TCO_2$ (mmhg) | High $CO_2$ $ETCO_2$ (mmhg) | Calm breathing $ETCO_2$ | | Low $CO_2$ $ETCO_2$ | | High $CO_2$ $ETCO_2$ | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Max | Min | *Max* | Min | Max | Min |
| Normal | 30 | 24.18±1.04 | 13.05±5.18 | 35.25±5.98 | 34.3 | 15.12 | 45.3 | 23 | 45.3 | 23 |
| Case | 42 | 22.86 ±8.03 | 13.26±7.53 | 32.59±8.58 | 58.50 | 13.12 | 69.1 | 20 | 69.1 | 20 |
| Lateral MCA stenosis | 18 | 22.75±2.51 | 13.45±2.40 | 32.29±2.59 | 58.5 | 13.12 | 50.60 | 4.40 | 58.50 | 13.12 |
| Multi-vessel stenosis | 24 | 22.95±5.54 | 13.12±4.91 | 32.81±6.48 | 38.00 | 14.70 | 23.50 | 4.90 | 38.00 | 14.70 |

side was defined as the vascular stenosis side; while the healthy side was defined as the non-stenosis side. The multiple vascular stenosis group: with two or more intracranial vessel stenosis, and (or) intra- and extracranial vascular occlusion. According to the degrees of left and right intra- and extracranial vascular lesions shown by TCD or DSA, involved number and clinical symptoms at this admission, the lesion sides were divided into the severer lesion side and the lighter lesion side.

The patients' CVR values were compared with the left and right CVR values of the normal control group, respectively (**Table 1**). ① There existed the difference in the dilation reserve among the lesion side of lateral MCA stenosis group, the heavier side of multi-vessel stenosis group and the normal group ($F = 3.755$, $P<0.05$), and that of the heavier side of multi-vessel stenosis group was significantly lower than the normal group ($t = -2.546$, $P<0.05$). ② There existed the difference in the overall reserve among the lesion side of lateral MCA stenosis group, the heavier side of multi-vessel stenosis group and the normal group ($F = 5.894$, $P<0.01$), and that of the heavier side of multi-vessel stenosis group was significantly lower than the normal group ($t = -3.357$, $P<0.01$); and that of the heavier side of multi-vessel stenosis group was significantly lower than the lesion side of lateral MCA stenosis group ($t = 2.471$, $P<0.05$).

*The comparison of end-expiratory $CO_2$ partial pressure values among the case group*

The lateral MCA stenosis group and the multi-vessel stenosis group with the control group, as well as among the various groups, showed no significant difference (F were 0.297, 0.956, 1.075, $P>0.05$) (**Table 2**).

*Correlation analysis*

The 42 patients of the case group were divided into the mild and severe degree according to the vascular lesion degrees: Mild: lateral MCA stenosis; Severe: multi-vessel stenosis. The vascular lesion degrees were negatively correlated to the dilation reserve values and the overall reserve values, respectively ($r = -0.322$, $P<0.05$; $r = -0.364$, $P<0.05$); while exhibited no significant correlation with the constriction reserve values ($r = -0.294$, $P>0.05$).

## Discussion

In this study, TCD was performed to measure the arterial blood flow velocity changes in the induced hypercapnia and hypocapnia, and then to monitor the end-expiratory $CO_2$ concentration for the correction and evaluating the cerebrovascular response and reserve capacities. The study found that the values of contraction reserve, dilation reserve and overall reserve of the diseased and healthy sides of the lateral MCA stenosis group had no significant difference with those of the normal group, according to the cerebral ischemia dynamic study by Derdeyn et al [15], CVR could be divided into three phases: phase 0: normal hemodynamic status; phase 1: because the cerebral perfusion pressure decreased, and the collateral circulation was insufficient, the reflex vasodilation occurred, and in this phase, the cerebral blood volume increased, and the mean transit time extended, while the cerebral blood flow and oxygen extraction fraction remained unchanged; phase 2: the cerebral perfusion was insufficient, the cerebral blood flow decreased while the oxygen extraction fraction increased. The collateral circulation opened in the early stage of chronic low perfusion, when it was still not enough for the compensation, the cerebral small artery would dilate, CVR mechanism began to act, when the cerebral small arterial dilation was still unable to maintain the needs of cerebral tissue perfusion, namely when the CVR mechanism lost the compensation, the oxygen extraction fraction began to increase, and the cerebral metabolic reserve mechanism came into act, when the cerebral metabolic reserve mechanism also lost the compensation, the stroke would occur. The stenosis situation in the lateral MCA stenosis group was mainly mild (77.8%), the blood flow was blocked, the hemodynamic changes were not significant, the remote blood supply area did not occur the hypoperfusion, thus the reduction of CVRI value was not obvious, even some patients exhibited the increased CVRI values, and that of the diseased side was higher than the healthy side, in this situation, the body's CVR might play the functional roles. The dilation reserve and overall reserve of the severer-lesion side in the multi-vessel stenosis group were lower than the normal control group ($P<0.05$, $P<0.01$), and also significantly reduced than the lateral MCA stenosis group ($P<0.05$, $P<0.01$). With the increased severities of stenosis, or associated with the multi-vessel disease or occlusion, the distal cerebral blood flow would then be reduced, in order to maintain the brain tissue metabolism under the ischemia and hypoxia, the cerebral small arteries would dilate, the vascular resistance would then decrease so that the blood supply might increase, when the blood $CO_2$ partial pressure was artificially induced increasing, the dilation ability of small blood vessels at the distal end of stenosis would reduce and could no longer expand, thus the increase rate of cerebral blood flow velocity, which flew through the stenotic blood vessels, would reduce, and the cerebrovascular reserve and reactivity fell, no longer responding to the $CO_2$ stimulation, and the regulatory function was depleted. These results suggested that the disease aggravated, the more obvious CVR declined, the more indexed involved [16].

The study also studied the correlation between the vascular disease degrees and CVR, and found that the more severe degrees of vascular stenosis, the more vessels involved, and the worse CVR. because the blood flow was blocked, the hemodynamics changed, the remote blood supply area was in the low perfusion state because of the absence of effective collateral circulation compensation [17], with the blockage of blood flow increased, the distal cerebral blood flow reduced, in order to maintain the brain tissue metabolism under the ischemia and hypoxia, the cerebral small arteries would dilate, the vascular resistance would then decrease so that the blood supply might increase, when the blood $CO_2$ partial pressure was artificially induced increasing, the dilation ability of small blood vessels at the distal end of stenosis would reduce, the increase rate of cerebral blood flow velocity, which flew through the stenotic blood vessels, would reduce, and the cerebrovascular reserve and reactivity fell, no longer responding to the $CO_2$ stimulation [18]. The evaluation and screening towards the CVR impaired patients would help the clinic to adopt the appropriate treatment measures earlier to prevent the stroke, thus CVR also had an important value towards the ischemic stroke prognosis [19, 20]. Therefore, the combined methods of TCD and $ETCO_2$ could help to evaluate the cerebrovascular reactivity of intracranial stenosis patients under the hypercapnia and hypocapnia, measure the cerebrovascular reserve capacity, thus assessing whether the risk of low perfusion stroke would occur towards the vascular stenosis patients, the more severe the stenosis, the worse the CVR reserve capacity, and the eventual risk of hypoperfusion stroke occurrence would be greater.

## Disclosure of conflict of interest

None.

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