Neurosci Bull December 1, 2012, 28(6): 723–728. http://www.neurosci.cn
DOI: 10.1007/s12264-012-1282-y

·Original Article·

Compromised cerebrovascular modulation in chronic anxiety: evidence from cerebral blood flow velocity measured by transcranial Doppler sonography

Hong-Liang Zhang[1,*], Zhen-Ni Guo[2,*], Ge Yang[3], Le Yang[1], Ke Han[2], Jiang Wu[1], Yingqi Xing[2], Yi Yang[1]

[1]*Department of Neurology,* [2]*Center for Neurovascular Ultrasound, The First Norman Bethune Hospital of Jilin University, Changchun 130021, China*

[3]*Department of Geriatric Medicine, The Affiliated Hospital of Changchun University of Chinese Medicine, Changchun 130000, China*

Abstract: Objective Cerebral autoregulation (CA) is the mechanism by which constant cerebral blood flow is maintained despite changes in cerebral perfusion pressure. CA can be evaluated by dynamic monitoring of cerebral blood flow velocity (CBFV) with transcranial Doppler sonography (TCD). The present study aimed to explore CA in chronic anxiety. **Methods** Subjects with Hamilton anxiety scale scores ≥14 were enrolled and the dynamic changes of CBFV in response to an orthostatic challenge were investigated using TCD. **Results** In both the anxious and the healthy subjects, the mean CBFV was significantly lower in the upright position than when supine. However, the CBFV changes from supine to upright differed between the anxious and the healthy groups. Anxious subjects showed more pronounced decreases in CBFV with abrupt standing. **Conclusion** Our results indicate that cerebrovascular modulation is compromised in chronic anxiety; anxious subjects have some insufficiency in maintaining cerebral perfusion after postural change. Given the fact that anxiety and impaired CA are associated with cardiovascular disease, early ascertainment of compromised cerebrovascular modulation using TCD might suggest interventional therapies in the anxious population, and improve the primary prevention of cardiovascular disease.

Keywords: cardiovascular dysautonomia; cerebral blood flow velocity; anxiety; transcranial Doppler sonography

1 Introduction

Cerebral autoregulation (CA) is the mechanism by which constant cerebral blood flow is maintained despite changes in cerebral perfusion pressure. Cardiovascular dysautonomia is common in patients with anxiety[1,2]. Yeragani *et al.* found significantly decreased vagal and increased sympathetic activity, decreased arterial compliance and possible atherosclerotic changes, and increased blood pressure in patients with anxiety[3]. Short-term cardiovascular responses to the postural change from sitting to standing involve complex interactions between the autonomic nervous system, which regulates blood pressure, and CA, which maintains cerebral perfusion. Transcranial Doppler sonography (TCD) is an efficient tool to assess the blood flow velocity within the cerebral

*These authors contributed equally to this work.
Corresponding authors: Yi Yang, Yingqi Xing
Tel: 86-431-88782762; Fax: 86-431-88782378
E-mail: doctor_yangyi@hotmail.com; xingyq@sina.com
Article ID: 1673-7067(2012)06-0723-06
Received date: 2012-03-09; Accepted date: 2012-05-01

vessels and CA in both physiological states and pathological conditions[4]. Dynamic monitoring of cerebral blood flow velocity (CBFV) with TCD can reveal the status of CA after an orthostatic challenge[5,6].

In our previous clinical practice, we observed significant decreases in CBF after active standing in 7 of 10 anxious patients[7]. Orthostatic hypotension, which refers to an insufficiency in regulating blood pressure even to a subsyndromal degree in response to an orthostatic challenge, has been reported in anxiety-like disorders[8]. In the present study, we assessed cerebrovascular modulation in chronic anxiety, as measured by the TCD CBFV curve.

2 Subjects and methods

2.1 Participants Twenty-five consecutive patients with chronic anxiety [Hamilton anxiety scale (HAMA) score ≥14] recruited in the outpatient unit, Department of Neurology, the First Hospital of Jilin University, from July 2010 to December 2010, participated in this study. "Chronic" was defined as having typical anxiety symptoms for >3 months. Enrolled subjects were otherwise healthy, with no ascertained disorders in the nervous, cardiovascular or respiratory systems. Subjects denied exposure to psychotropic or vasoactive medications within one month before screening. Subjects with stenotic intracranial or extracranial arteries diagnosed with TCD (EMS-9, Delica, China) and carotid ultrasound (IU22, Phillips, Andover, MA) were excluded. Twenty-five age- and sex-matched medically and psychiatrically healthy volunteers (HAMA score ≤6) were recruited as controls from healthy individuals undergoing routine health examination in our department. Informed consent was given by all participants. The clinical workup consisted of a thorough physical examination, electrocardiography, laboratory tests including liver and kidney function tests and hematology profile, and a cranial CT scan. Mental health status was evaluated by two unbiased clinical psychiatrists. Cognitive impairment was assessed with the Mini-Mental State Examination.

2.2 TCD protocol The TCD (MultiDop X4, DWL, Sipplinghen, Germany) protocol basically accorded with that described previously[9]. Briefly, the mean CBFV in the unilateral or bilateral middle cerebral artery at a depth of 50–60 mm was recorded with a 2-MHz probe through the temporal window, and the mean CBFV was obtained directly from the built-in software. The real-time blood flow spectrum was recorded simultaneously. Blood pressure was measured with a manual sphygmomanometer in the supine position and 2 min after standing. The pulse pressure was calculated from the difference between the systolic and diastolic pressures. The mean arterial pressure (MBP) was calculated according to the formula: MBP = diastolic pressure + 1/3 pulse pressure. The CBFV curve was dynamically recorded from the supine position (for 3 min) to the upright position (for 2 min), then to the supine position (for another 3 min). The whole protocol was completed within 15 min.

2.3 Statistics Data are presented as mean ± SEM. The statistical program for social sciences 12.0 (SPSS, IBM, West Grove, PA) was used for all data. Student's *t*-test or the Mann-Whitney U test was used to compare values between groups. All tests were two-tailed, and the level of significance was set to $P<0.05$.

3 Results

3.1 Demographic information A total of 25 consecutive patients with chronic anxiety (HAMA score, 19.7 ± 5.2; age, 46 ± 14 years; 2 males and 23 females) were enrolled in the study. Twenty-five age- and sex-matched medically and psychiatrically healthy volunteers (HAMA score, 3.8 ± 1.7; age, 46 ± 15 years; 6 males and 19 females) served as controls. The demographic features of the participants are listed in Table 1. MBP values did not differ between the supine and upright positions in both groups ($P>0.05$).

3.2 TCD findings The typical CBFV curves of healthy controls had two high plateau sections and one intermediate lower plateau section. When a healthy subject stood abruptly, the CBFV curve descended sharply to a lower level, followed by a rapid rebound to the same level as the supine baseline curve or even higher, forming a peak, and then descended and was maintained at a lower level than the supine baseline. The lower section of the curve was

Table 1. Demographic features and TCD data

	Anxiety group					Control group				
Subjects S	ex	Age(years)H	s coreC	BFV(cm/s)M (supine/upright)	BP(mm/Hg)S (supine/upright)	ex	Age(years)H	s coreC	BFV(cm/s)M (supine/upright)	BP(mm/Hg) (supine/upright)
1	M	46	23	79/68	110/109	F	53	3	75/78	87/89
2	F	50	20	51/35	87/88	F	68	5	37/33	87/86
3	F	62	14	73/76	114/107	M	5	5	50/53	85/86
4	F	61	18	65/50	92/85	F	52	2	75/77	109/100
5	F	21	16	63/63	77/81	M	42	6	52/49	93/93
6	F	78	16	42/38	91/74	F	29	2	79/71	81/90
7	F	54	29	60/53	92/91	F	30	3	59/63	77/83
8	F	47	32	50/30	93/83	F	35	1	75/70	89/89
9	F	66	15	59/54	93/90	F	31	3	65/68	88/92
10	F	47	20	60/52	95/90	F	70	4	70/67	86/78
11	F	46	14	50/48	84/80	F	50	4	77/73	83/87
12	F	44	20	74/59	90/87	F	25	6	55/47	91/87
13	F	36	15	76/68	82/90	F	36	6	45/50	99/100
14	F	54	17	43/25	78/80	F	23	1	79/74	77/73
15	F	39	18	53/50	91/93	F	70	5	51/47	85/80
16	M	54	19	52/48	92/88	F	57	4	75/71	93/97
17	F	25	19	76/48	76/78	M	55	5	46/38	107/115
18	F	22	20	71/59	97/99	F	28	2	78/73	95/90
19	F	38	30	71/53	73/73	F	50	4	69/63	105/97
20	F	27	22	77/45	91/93	F	50	1	40/37	87/87
21	F	42	18	55/43	98/97	F	61	2	44/41	83/89
22	F	56	18	78/66	88/91	M	58	5	48/40	88/89
23	F	54	29	50/36	83/92	M	48	5	50/40	95/100
24	F	42	14	53/50	83/99	M	53	6	60/55	96/87
25	F	50	16	76/80	89/93	F	20	4	39/35	73/70

CBFV, mean cerebral blood flow velocity; F: female; H score, Hamilton anxiety scale score; M: male; MBP, mean arterial blood pressure.

more pronounced in the anxiety group than in the control group (Fig. 1).

The mean CBFV values from the anxiety *versus* control groups in the supine and upright positions are listed in Table 1. The baseline supine and orthostatic CBFV values did not differ between the anxiety and the healthy groups (62.28 ± 11.96 cm/s *versus* 59.72 ± 14.44 cm/s, $P > 0.05$; 51.88 ± 13.60 cm/s *versus* 56.52 ± 15.11 cm/s, $P > 0.05$). In both groups, the mean CBFV was lower in the upright than in the supine position (both $P < 0.01$, Fig. 2). However, the CBFV changes from supine to upright position differed between the two groups. The anxiety group displayed more marked CBFV changes than the control group (10.40 ± 8.87 cm/s *versus* 3.20 ± 4.20 cm/s, $P < 0.01$, Fig. 3).

4 Discussion

Our cross-sectional study revealed that the dynamic CBFV curve, an index of cardiocerebrovascular modu-

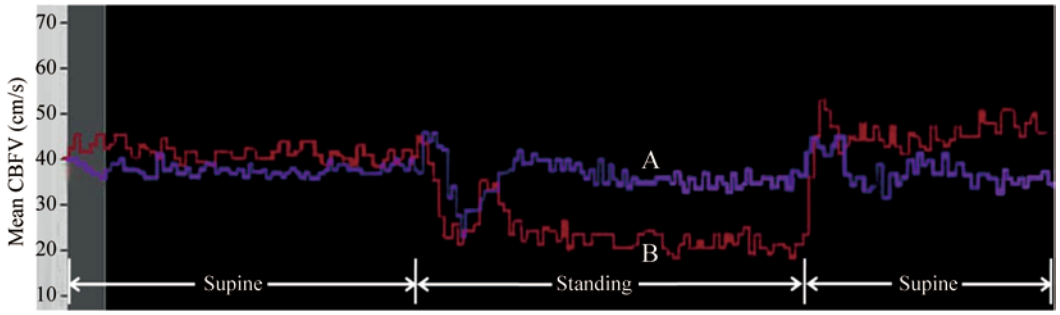

Fig. 1. Distinctive CBFV curves in healthy control (purple curve) and anxious (red curve) subjects. The curve was dynamically recorded by TCD from the supine position (for 3 min) to the upright position (for 2 min), then to the supine position (for 3 min). The typical curve of healthy control was formed by two high plateau sections and one intermediate lower plateau section (curve A). When a subject stood abruptly, the CBFV curve descended sharply to a lower level, followed by a rapid rebound to the same level as the supine baseline curve or even higher, forming a peak, and then descended and was maintained to a lower level than the supine baseline. The lower section of the curve was more pronounced in the anxiety group (curve B) than in the control group (curve A).

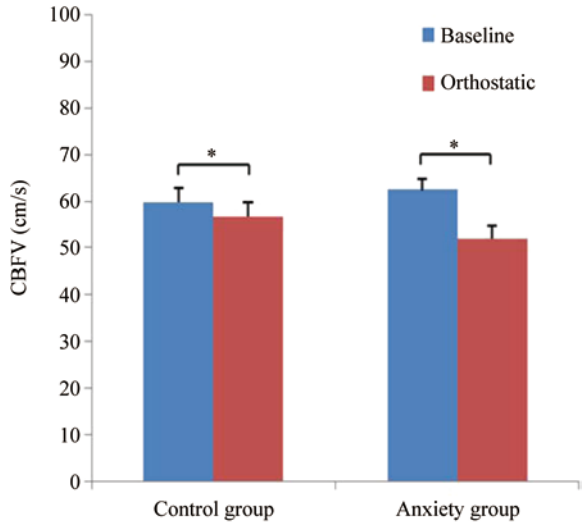

Fig. 2. CBFV values in supine and upright positions in control and anxiety groups. The baseline supine CBFV values did not differ between the healthy and anxiety groups (P >0.05). In both groups, the mean CBFV was lower in the upright than in the supine position (both *P <0.01).

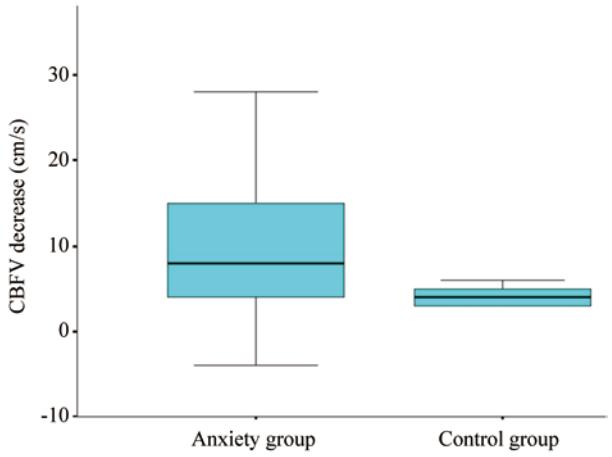

Fig. 3. Changes of CBFV values in response to orthostatic challenge. The CBFV curve was dynamically recorded by TCD from the supine position (for 3 min) to the upright position (for 2 min), then to the supine position (for 3 min). The CBFV changes from supine to upright differed between the two groups. The anxiety group displayed greater CBFV changes than the control group (P <0.01).

lation, was compromised in chronic anxiety. The curve changed with active standing and the mean CBFV values were significantly reduced in the upright position compared with the supine position, with a more marked change in subjects with anxiety. Our preliminary results indicate that the CBFV curve has specific features in anxiety. On one hand, the curve seems promising in screening for anxiety disorders in clinical practice. On the other hand, rapid identification of compromised CA in anxiety with TCD may suggest targeted treatment in clinical settings. The characteristic CBFV curve may help to make a diagnosis of anxiety.

This study is not the first to report cardiovascular dysautonomias in anxiety disorders. But we, for the first time, used dynamic CBFV monitoring to evaluate

cerebrovascular modulation in chronic anxiety. Cardiocerebrovascular responses to postural change from supine to standing involve complex interactions to maintain cerebral perfusion. Although the underlying mechanisms are not fully understood[5], two mechanisms might be involved: (1) autonomic regulation mediated by sympathetic and parasympathetic responses, which regulates heart rate, cardiac contractility, resistance and compliance, and (2) CA responses to local changes of myogenic tone, metabolic demand and CO_2 concentration, which affect cerebrovascular resistance[5]. Cardiovascular dysautonomia may also cause blood pressure changes in response to an orthostatic challenge, hence leading to CBFV changes. We thus measured blood pressure, to adjust for its confounding property. We found that MBP did not differ between the supine and upright positions in both groups. Therefore, we ascribe the findings in the anxious population to cardiovascular dysautonomia and localized it to the brain, rather than the whole cardiovascular system.

Upon abrupt postural change, cardiocerebrovascular modulation helps to maintain a constant cerebral blood flow in healthy people, whereas anxious people seem to have some insufficiency in maintaining cerebral perfusion after postural change; the autoregulation in response to local changes of myogenic tone, metabolic demand and CO_2 concentration in the brain might be compromised in anxiety.

During the past decades, several paradigms have been developed to study dynamic CA by measuring CBFV with TCD in response to postural changes. CA is often severely disturbed in occlusive carotid artery disease. Impaired CA is an important risk factor for stroke or transient ischemic attack in patients with symptomatic or asymptomatic carotid artery stenosis or occlusion[10]. There appears to be a link between impaired cerebrovascular reactivity and a risk of ischemic events ipsilateral to severe asymptomatic carotid stenosis[11]. Severely reduced CA predicts the risk of ipsilateral stroke and transient ischemic attack in patients with carotid occlusion, and to a lesser extent in asymptomatic carotid stenosis[12]. CA in patients with carotid stenosis is reduced compared with controls and improves significantly after carotid endarterectomy[13].

Symptoms of anxiety and depression are independent predictors of cardiovascular events[14]. The implications of comorbidity between anxiety and cardiovascular disease include higher morbidity, functional deficits, increased cardiovascular risk, and poor adherence to cardiac rehabilitation or exercise programs[15]. A study performed in a psychiatric hospital showed that those suffering from anxiety had a mortality rate for cardiovascular causes that was double than expected compared with non-anxious patients of the same age group, gender and time of hospitalization[16]. The presence of anxiety is an independent risk factor for cardiovascular disease, as a trigger either for acute myocardial infarction or for morbidity/mortality from cardiovascular causes[17,18]. The underlying mechanisms of the increased risk in patients with anxiety remain largely unknown[19]. Our findings indicate that anxiety leads to impairment of CA, hence conferring an increased risk for cardiovascular disease. Since the diagnosis of anxiety disorders is primarily dependent on symptoms, subjective bias cannot be ruled out in clinical practice. The compromised cerebrovascular modulation as detected in the present study highlights the importance of objective measures such as CBFV by TCD in the diagnosis of anxiety disorders. Nevertheless, early ascertainment of CA impairment might suggest intervention therapies in anxious population, so as to improve the primary prevention of cardiovascular disease. In addition, in our latest studies, we found that the CBFV curve returns to normal after anxiolytic therapy (such as Flupentixol and Melitracen)[20]. Further studies are ongoing to explore the effects of anti-anxiety medications.

However, the small sample size is a limitation of our study. Besides, the association of the altered CBFV curve with anxiety does not necessarily mean causation. Moreover, the anxious subjects in our study were recruited in the Department of Neurology. This selection bias may possibly challenge the generalizability of our findings.

In summary, dynamic monitoring of the CBFV curve from the middle cerebral artery showed that cerebrovascular modulation is impaired in chronic anxiety. The altered

CBFV curve might be a characteristic change in anxiety. Further studies are needed to explore the causal relations between CBFV curve and anxiety, the specificity and sensitivity of CBFV changes in anxiety, and the potential of the CBFV curve in the diagnosis of anxiety disorders.

Acknowledgments: Statistical analyses were performed by Associate Professor Yuchun Tao from the College of Public Health, Jilin University, Changchun, China. Mental health status was evaluated by Drs. Yan Huang and Siyuan He from the First Hospital of Jilin University, Changchun, China. This work was supported by grants from China Scholarship Council.

References:

[1] Hasler G, Fromm S, Alvarez RP, Luckenbaugh DA, Drevets WC, Grillon C. Cerebral blood flow in immediate and sustained anxiety. J Neurosci 2007, 27: 6313–6319.

[2] Licht CM, de Geus EJ, van Dyck R, Penninx BW. Association between anxiety disorders and heart rate variability in The Netherlands Study of Depression and Anxiety (NESDA). Psychosom Med 2009, 71: 508–518.

[3] Yeragani VK, Tancer M, Seema KP, Josyula K, Desai N. Increased pulse-wave velocity in patients with anxiety: implications for autonomic dysfunction. J Psychosom Res 2006, 61: 25–31.

[4] Willie CK, Colino FL, Bailey DM, Tzeng YC, Binsted G, Jones LW, *et al.* Utility of transcranial Doppler ultrasound for the integrative assessment of cerebrovascular function. J Neurosci Methods 2011, 196: 221–237.

[5] Olufsen MS, Ottesen JT, Tran HT, Ellwein LM, Lipsitz LA, Novak V. Blood pressure and blood flow variation during postural change from sitting to standing: model development and validation. J Appl Physiol 2005, 99: 1523–1537.

[6] Panerai RB, Dawson SL, Eames PJ, Potter JF. Cerebral blood flow velocity response to induced and spontaneous sudden changes in arterial blood pressure. Am J Physiol Heart Circ Physiol 2001, 280: H2162–2174.

[7] Guo ZN, Xing Y, Yang L, Huang Y, Zhang L, Luan SX, *et al.* Elementary study about the supine-standing cerebral blood flow in patients with anxiety. J Apoplexy Nerv Dis 2011, 28: 50–52. [Article in Chinese]

[8] Czajkowska J, Ozhog S, Smith E, Perlmuter LC. Cognition and hopelessness in association with subsyndromal orthostatic hypotension. J Gerontol A Biol Sci Med Sci 2010, 65: 873–879.

[9] Xu WH, Wang H, Wang B, Niu FS, Gao S, Cui LY. Disparate cardiocerebral vascular modulation during standing in multiple system atrophy and Parkinson disease. J Neurol Sci 2009, 276: 84–87.

[10] Diehl RR. Cerebral autoregulation studies in clinical practice. Eur J Ultrasound 2002, 16: 31–36.

[11] Silvestrini M, Vernieri F, Pasqualetti P, Matteis M, Passarelli F, Troisi E, *et al.* Impaired cerebral vasoreactivity and risk of stroke in patients with asymptomatic carotid artery stenosis. JAMA 2000, 283: 2122–2127.

[12] Markus H, Cullinane M. Severely impaired cerebrovascular reactivity predicts stroke and TIA risk in patients with carotid artery stenosis and occlusion. Brain 2001, 124: 457–467.

[13] Mense L, Reimann M, Rüdiger H, Gahn G, Reichmann H, Hentschel H, *et al.* Autonomic function and cerebral autoregulation in patients undergoing carotid endarterectomy. Circ J 2010, 74: 2139–2145.

[14] Rutledge T, Linke SE, Krantz DS, Johnson BD, Bittner V, Eastwood JA, *et al.* Comorbid depression and anxiety symptoms as predictors of cardiovascular events: results from the NHLBI-sponsored Women's Ischemia Syndrome Evaluation (WISE) study. Psychosom Med 2009, 71: 958–964.

[15] Sardinha A, Araújo CG, Soares-Filho GL, Nardi AE. Anxiety, panic disorder and coronary artery disease: issues concerning physical exercise and cognitive behavioral therapy. Expert Rev Cardiovasc Ther 2011, 9: 165–175.

[16] Coryell W, Noyes R, Clancy J. Excess mortality in panic disorder. A comparison with primary unipolar depression. Arch Gen Psychiatry 1982, 39: 701–703.

[17] Walters K, Rait G, Petersen I, Williams R, Nazareth I. Panic disorder and risk of new onset coronary heart disease, acute myocardial infarction, and cardiac mortality: cohort study using the general practice research database. Eur Heart J 2008, 29: 2981–2988.

[18] Chen YH, Tsai SY, Lee HC, Lin HC. Increased risk of acute myocardial infarction for patients with panic disorder: a nationwide population-based study. Psychosom Med 2009, 71: 798–804.

[19] Frasure-Smith N, Lesperance F. Depression and anxiety as predictors of 2-year cardiac events in patients with stable coronary artery disease. Arch Gen Psychiatry 2008, 65: 62–71.

[20] Yang L, Yang Y, He SY, Xin ZE, Guo ZN. Use of transcranial Doppler sonography to evaluate patients with anxiety disorders before and after treatment. Chin J Lab Diagn 2012; 16: 1324–1325. [Article in Chinese]