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Collapsed Jugular Vein and abnormal cerebral blood flow changes in patients of Panic Disorder

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ABSTRACT

Objective: Panic disorder (PD) is characterized by panic attacks accompanied with respiratory symptoms. Internal jugular vein (IJV) alters its hemodynamics in response to respiration and which might cause cerebral blood flow (CBF) changes. In the present study, we compared (1) respiratory-related IJV hemodynamics and (2) CBF changes during Valsalva maneuver (VM) between PD and normal subjects.
Methods: 42 PD patients and age/gender-matched controls (14 men; 52.3 ± 11.4 years) were recruited. Duplex ultrasonography measured time-averaged mean velocity (TAMV) and lumen in IJV at baseline and deep inspiration. Lumen area <0.10 cm^2 at deep inspiration was defined as IJV collapse. CBF changes during VM were recorded by transcranial Doppler (TCD).
Results: Compared with normal group, PD patients had significantly higher frequency of IJV collapse at deep inspiration (Left: 40.0% vs. 7.0%, $p = 0.0003$, Right: 17.0% vs. 0%, $p = 0.0119$). IJV collapse was associated with symptoms of respiratory subtype in our PD patients. PD group also had smaller lumen (Left: 0.53 ± 0.29 vs. 0.55 ± 0.26 cm^2, $p = 0.8296$, Right: 0.63 ± 0.36 vs. 0.93 ± 0.45 cm^2, $p = 0.0014$) and slower TAMV of IJV at baseline (Left: 11.8 ± 8.43 vs. 20.6 ± 16.5 cm/s, $p = 0.0003$, Right: 15.9 ± 9.19 vs. 24.1 ± 15.7 cm/s, $p = 0.0062$). PD patients with inspiration-induced IJV collapse had more decreased CBF during VM compared with the other PD patients and normal individuals respectively.
Interpretation: We are the first to show that PD have less IJV flow at baseline and more frequent collapse at deep inspiration. Inspiration-induced IJV collapsed was associated with CBF decrement during VM in PD patients. These results suggest that venous drainage impairment might play a role in the pathophysiology of PD by influencing CBF.

1. Introduction

Panic disorder (PD) is characterized by recurring panic attacks accompanied with several autonomic and cardio-respiratory symptoms. (American Psychiatric Association, 2000) Dyspnea with following dizziness/fainting is a core feature of panic attacks and a common chief complaint of PD patients encountered in clinics. (Ley, 1985) The pathophysiology of PD is yet not understood though extensive observations and researches. Several abnormal respiratory-related physiologies have been found involved in the pathophysiology of PD, which include hyperventilation with hypocapnic alkalosis, underlying pulmonary diseases (e.g. COPD), increased central CO2 sensitivity, exaggerated cerebrovascular responses to hypocapnia, changes of the central rhythm generator, and dysfunctional opioid system sensitivity. Many of these

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researches focused on dysfunction of central or peripheral organs controlling respiration, or mechanisms of hyperventilation. Whether there are other abnormalities in organ/tissues which are normally (physiologically) associated with respiration involved in the pathophysiology of PD is still an open question. (Freire and Nardi, 2012; Nardi et al., 2004, 2009; Perna et al., 2004; Preter et al., 2011; Sinha et al., 2007).

Internal jugular vein (IJV) is the main pathway for cerebral venous drainage. Many neurological disorders are associated with abnormal IJV flow patterns. (Chung et al., 2006, 2011; Doepp et al., 2008; Hsu et al., 2008; Nedelmann et al., 2009; Zamboni et al., 2009) To elucidate the mechanisms, physiological studies showed that these abnormal IJV flow patterns impair cerebral venous drainage and cause consequent cerebral blood flow (CBF) decrement. (Chung et al., 2010; Wu et al., 2011) IJV lumen would vary at different status of respiration; (Burrows et al., 2003; Schaller, 2004) during inspiration, a negative intrathoracic pressure would increase the flow velocity of IJV and then, due to Bernoulli's principle, reduce the lumen of IJV. (Conn and O'Keefe, 2012; Lurie et al., 2002; Patel et al., 1999) A study found that subjects with more narrowed IJV lumen during anti-gravity straining maneuver had higher frequencies of gravity-induced loss of consciousness, presumably via decreased CBF resulting from impaired cerebral venous drainage. (Choi et al., 2010; Cirovic et al., 2000, 2001; Werchan et al., 1996) In the present study, we hypothesized that, compared with normal individuals, (1) patients with panic disorder have more narrowed IJV lumen at deep inspiration and (2) this IJV abnormality will influence CBF changes. These results will shed lights on the pathophysiology of PD: trying to explain its respiratory-related symptoms and mechanisms of abnormal CBF changes.

2. Subjects and methods

2.1. Subjects

PD patients were consecutively referred form psychological clinics of Taipei Veterans General Hospital (Dr. Hong) and screened for inclusion in the present study. PD was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV-TR) criteria. (American Psychiatric Association, 2000) Patients who were not willing to participate or having the histories of hypertension (HTN), diabetes, smoking, stroke, ischemic heart disease, congestive heart disease, arrthymia, pulmonary diseases, and malignancies were not eligible to be included. Extracranial duplex and transcranial color-coded Doppler ultrasonography (Sonos 5500, Hewlett Packard, Andover, MA, SA) were performed in all referred patients to exclude patients with carotid or intracranial artery stenosis. We also included age- and sex-matched healthy volunteers as control group. Taipei Veterans General Hospital's institutional review board approved the study proposal, and we have obtained written informed consent from all participants.

2.2. Symptom profiles

Symptoms of panic attacks were recorded in all patients of PD. Respiratory subtype of PD requires 4 of the following 5 symptom criteria during an individual's recent panic attack: choking or smothering sensations; shortness of breath; chest pain or discomfort; numbness or tingling sensations; and fear of dying. (Briggs et al., 1993).

2.3. Duplex ultrasonography for IJV hemodynamics assessment: velocity, lumen and the presence of reflux

Color-coded duplex sonography with a 7-MHz linear transducer (iU22; Philips MedicalSystems, Andover, MA, USA) was performed in all subjects by one technician who was blinded to subjects' characteristics. On examination, subjects were in a head-straight, flat supine position after a 10-min quiet rest. A luxury amount of ultrasound gel was used and great care was taken to avoid compression of neck veins during examination.

Time-average-mean velocity (TAMV) and lumen of IJV were recorded at 5 cm above the junction of the IJV and brachiocephalic vein. During acquisition of TAMV, the Doppler cursor was directed parallel to the vessel alignment, with the gate adjusted to comprise the entire lumen. TAMV measurements were made using built-in software (iU22; Philips) by including at least three cardiac cycles on the Doppler spectrum. The probe was then turned by 90° at the same site of IJV to measure the cross-sectional lumen. The cross-sectional lumen area was measured three times in B-mode image and then averaged for later analysis. Both lumen and TAMV were recorded at brief apnea after two respiratory statuses: (1) normal expiration (baseline), and (2) deep inspiration. All subjects were asked not to strain during breath-holding to avoid increasing intrathoracic pressure. We defined lumen area <0.10 cm^2 in IJV at deep inspiration as IJV collapse (Fig. 1). TAMV and cross-sectional lumen/diameter of internal carotid artery (ICA) and vertebral artery (VA) at baseline were also recorded at 1 cm distal to the carotid bifurcation and the middle of neck (V2) respectively. We did a reproducibility assessment of IJV parameter measurement on right IJV at baseline in 20 people (the intervals of twice measurements were one hour), which showed an excellent reproducibility (lumen: Cronbach's $\alpha = 0.994$; TAMV: Cronbach's $\alpha = 0.931$).

2.4. Transcranial Doppler for recording CBF changes during Valsalva maneuver

Transcranial Doppler (TCD) simultaneously recording middle cerebral artery flow velocity (MCAV) and arterial blood pressure (ABP) during VM is broadly used to evaluate CBF changes in response to cardiovascular effects of VM. (Pott et al., 2000; Wallasch and Kropp, 2012; Zhang et al., 2004) It is known that VM increases intrathoracic pressure, decreases cardiac output, decreases ABP and impairs jugular venous outflow. Therefore, CBF changes in response to ABP and altered cerebral venous drainage can be assessed by TCD during VM.

Bilateral MCAV was acquired by TCD (Multidop-X, DWL; Sipplingen, Germany). The transducers were fixed in place by a probe holder, and MCAV was continuously recorded at the depth of the best signal (44–55 mm). Instantaneous ABP was recorded non-invasively by servocontrolled infrared finger plethysgraphy (Finapres, model 2300, Ohmeda Monitoring Systems, Englewood, CT, U.S.A.). Heart rate was monitored by ECG during TCD recording. After at least 10 min of supine rest, two VM were performed with a 5-min interval between the two tests. The second VM was used for data analysis. The VM was performed lasting for 15 s with increased intrathoracic pressure 40 mmHg maintained. Before each VM, subjects would take a deep inspiration.

Beat-to-beat ABP and MCAV measured for 15 s before the VM were averaged as baseline. During VM, there are four phases of ABP and MCAV changes on TCD. (Greenfield et al., 1984; Tiecks et al., 1995, 1996) Relative changes in ABP and CBF (represented by MCAV changes) in each phase during VM were calculated as the ratio of the magnitude of the phasic changes divided by the baseline measurements.

None of the subject was allowed taking any medication known to affect the cardiovascular system before examinations. Selective serotonin reuptake inhibitors, tricyclic antidepressants, and Benzodiazepines were discontinued for at least 5 half-lives before the examination. Caffeine-containing products, nicotine, and alcohol were also avoided for at least 12 h before the study. All subjects