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Cerebral blood flow autoregulation is impaired in schizophrenia: A pilot study

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ABSTRACT

Patients with schizophrenia have a higher risk of cardiovascular diseases and higher mortality from them than does the general population; however, the underlying mechanism remains unclear. Impaired cerebral autoregulation is associated with cerebrovascular diseases and their mortality. Increased or decreased cerebral blood flow in different brain regions has been reported in patients with schizophrenia, which implies impaired cerebral autoregulation. This study investigated the cerebral autoregulation in 21 patients with schizophrenia and 23 age- and sex-matched healthy controls. None of the participants had a history of cardiovascular diseases, hypertension, or diabetes. All participants underwent 10-min blood pressure and cerebral blood flow recording through finger plethysmography and Doppler ultrasonography, respectively. Cerebral autoregulation was assessed by analyzing two autoregulation indices: the mean blood pressure and cerebral blood flow correlation coefficient (Mx), and the phase shift between the waveforms of blood pressure and cerebral blood flow determined using transfer function analysis. Compared with the controls, the patients had a significantly higher Mx (0.257 vs. 0.399, $p = 0.036$) and lower phase shift (44.3° vs. 38.7° in the 0.07–0.20 Hz frequency band, $p = 0.019$), which indicated impaired maintenance of constant cerebral blood flow and a delayed cerebrovascular autoregulatory response. Impaired cerebral autoregulation may be caused by schizophrenia and may not be an artifact of coexisting medical conditions. The mechanism underlying impaired cerebral autoregulation in schizophrenia and its probable role in the development of cerebrovascular diseases require further investigation.

1. Introduction

Schizophrenia affects approximately 1% of the population. The affected population has higher mortality and a 20% shorter life span than does the general population (Brown, 1997). This gap has increased in recent years (Saha et al., 2007). Cardiovascular diseases, including ischemic heart disease and cerebrovascular diseases, are the major causes of death other than suicide or injury in patients with schizophrenia (Bushe et al., 2010; Curkendall et al., 2004; Olfson et al., 2015). Furthermore, both the incidence of cardiovascular diseases and the associated mortality are about 2 times higher in patients with schizophrenia than in the general population (Curkendall et al., 2004; Lin et al., 2008).

Previous studies have reported that cardiovascular diseases in patients with schizophrenia reduced their life span by 15–20 years (Nordentoft et al., 2013). Factors such as underlying psychiatric illnesses, medications, metabolic syndrome, life habits, and the availability and accessibility of medical services have been proposed to explain the high incidence and mortality rate of cardiovascular diseases in patients with schizophrenia; however, the exact reason remains uncertain. It has generally been believed that antipsychotic medications account for the development of metabolic syndrome (Zimmermann et al., 2003). However, mortality from cardiovascular diseases in schizophrenic patients is not proportional to their cumulative exposure to antipsychotics (Torniainen et al., 2015). Furthermore, use of second-

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generation antipsychotics typically results in a higher rate of metabolic syndrome but not in higher morbidity and mortality from cardiovascular diseases than does use of first-generation antipsychotics (Bushe et al., 2010). Therefore, factors other than medications and metabolic syndrome may be responsible for the development of cardiovascular diseases in patients with schizophrenia.

Studies using positron emission tomography (PET) or single photon emission computed tomography have revealed that schizophrenia increases or decreases the resting-state cerebral blood flow (CBF) in many brain regions (Andreasen et al., 1997; Kanahara et al., 2013; Malaspina et al., 2004), and alterations in the resting-state CBF have been associated with the clinical symptoms of schizophrenia through PET or perfusion magnetic resonance imaging (Lahti et al., 2006; Zhu et al., 2015). Furthermore, studies involving transcranial Doppler ultrasonography revealed that patients with schizophrenia had smaller CBF changes while performing tasks than did healthy controls (Owega et al., 1998; Sabri et al., 2003; Schuepbach et al., 2002). Therefore, it appears that the mechanism of maintaining an adequate CBF is impaired in patients with schizophrenia.

Cerebral autoregulation (CA) is a physiological mechanism for maintaining adequate CBF despite changes in blood pressure (BP) (van Beek et al., 2008). The brain is a high-blood-demand organ because of its high energy consumption, and impaired CA results in cerebral hypo- or hyperperfusion, which could affect the pathogenesis or outcome of neurological diseases. CA is assessed by analyzing the correlation between CBF and BP. In the current study, we used Doppler ultrasonography and finger plethysmography to record changes in CBF and peripheral BP, respectively. The test was conducted when the participants were in the resting state with spontaneous fluctuations in CBF and BP. The advantage of this method is its acceptable reliability and validity. Standard testing protocols have been recommended on the basis of a consensus among experts (Claassen et al., 2016). Presumably, during spontaneous fluctuations in CBF and BP, the changes in CBF are smaller and restored faster than those in BP in participants with intact CA.

Impaired CA has been observed in cerebrovascular diseases, such as ischemic stroke, hemorrhagic stroke, and carotid artery stenosis (Otite et al., 2014; Petersen et al., 2015; Reinhard et al., 2005; Reinhard et al., 2003; Reinhard et al., 2008). Furthermore, impaired CA has been observed in traumatic brain injury (Czosnyka et al., 1996), migraine with aura (Reinhard et al., 2008), and Alzheimer's disease (den Abeelen et al., 2014). Vascular dysfunction and an increased risk of stroke have been observed in migraine and Alzheimer's disease (Chi et al., 2013; Hu et al., 2016). In a study on subarachnoid hemorrhage, patients with worse CA had a higher risk of secondary vasospasm and cerebral ischemia than did patients with better CA (Otite et al., 2014). Therefore, impaired CA is associated with an increased risk of subsequent cerebral ischemia.

The changes in CBF in patients with schizophrenia are different from those in healthy people, implying the impairment of CA in patients with schizophrenia. Furthermore, impaired CA is associated with the risk of subsequent cerebrovascular diseases, which may explain the higher incidence of cerebrovascular diseases in patients with schizophrenia than in healthy people. However, a study providing evidence of impaired CA in patients with schizophrenia is thus far unavailable. In this study, CA was compared between patients with schizophrenia and healthy people. Specifically, we hypothesized that in a resting state with spontaneous CBF and BP fluctuations, the changes in CBF in patients with schizophrenia would be larger and slower than those in healthy people.

2. Methods

2.1. Participants and clinical assessment

This study was approved by the Institutional Review Board of Taipei Medical University, and all participants provided written informed consent. Patients with a diagnosis of schizophrenia at the outpatient clinic, at the day-care unit, or just before discharge from acute psychiatric ward at Taipei Medical University, Shuang Ho Hospital were enrolled in this study. Each patient was in a stable psychiatric condition. None of the patients had a history of cardiovascular diseases. Healthy volunteers without a history of cardiovascular diseases, mood disorders, or sleep disorders were recruited from the community as controls. The controls did not use any medicine when the study was conducted. By contrast, the patients with schizophrenia used several types of medicines including antipsychotics, antidepressants, mood stabilizers, and hypnotics. The medicines of the patients are listed in Supplementary Table 1. The participants were instructed not to consume caffeinated drinks or heavy meals on the day of the CA test.

The diagnoses of the patients were confirmed by trained psychiatrists using a structured psychiatric diagnostic interview according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM- IV-TR). None of the patients reported a history of substance dependence within 6 months prior to the study, electroconvulsive therapy within 6 months prior to the study, or head injury with consciousness loss. The psychiatric condition of each patient was evaluated by trained psychiatrists according to the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

2.2. Cerebral autoregulation assessment

In this study, the protocol of CA assessment, consisting of signal acquisition, signal processing, and algorithm analysis, was performed according to the white paper of the International Cerebral Autoregulation Research Network (CARNet) (Claassen et al., 2016). In brief, each participant was tested in the supine position with a head elevation of 30° and spontaneous breathing. Signals were recorded after a 15-min rest, and a stable end-tidal carbon dioxide (CO_2) level was confirmed through capnography (Nellcor N85, Medtronic, USA) because changes in CO_2 levels in blood can affect CBF; however, the data of end-tidal CO_2 levels were not used in the CA algorithm. Beat-to-beat BP was noninvasively recorded through finger plethysmography (Finometer Pro, Finapres, the Netherlands). CBF was assessed by continuously recording the blood flow velocity (BFV) in the extracranial internal carotid artery (ICA) by using a Doppler ultrasonographic monitoring system (MultiDop-T, DWL, Germany) with two 2-MHz probes fixed on the upper neck and an insonation depth of 40–50 mm. The BP and BFV were digitally recorded simultaneously for 10 min for each participant at a sampling rate of 50 Hz by using a laptop computer equipped with a data acquisition device (NI USB-6221 BNC, National Instruments, USA) and signal processing software (DataDemon, DynaDx, USA).

Two methods were applied for evaluating CA: calculation of the mean BP and mean BFV correlation coefficient (Mx) and transfer function analysis (TFA). Mx was calculated as follows: Pearson's correlation coefficients between 20 consecutive 3-s periods (1 min) of mean BP and mean BFV were calculated, and the 10 correlation coefficients of 10 min were averaged (Czosnyka et al., 1996; Reinhard et al., 2003). The rationale behind using Mx as a CA index is that the change in BFV is considered independent of the change in BP in people with intact CA; therefore, Mx = 0 represents intact CA, whereas Mx = 1 represents absent CA. TFA is a frequency domain analysis that calculates the "phase shift" and "gain" between the cerebral BFV and BP waveforms 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) (Claassen et al., 2016). The CA algorithm used in this study was obtained from the website of CARNet (http://www.car-net.org/content/resources). Under normal physiological conditions, spontaneous oscillations are observed in cerebral BFV and BP even when an individual is in a resting state. The changes in cerebral BFV are generally restored faster than those in BP in people with intact CA, resulting in a phase shift between the waveforms of cerebral BFV and BP. Furthermore, the gain indicates that CA attenuates the change in BFV compared with that in BP; therefore, a low gain represents efficient CA (van Beek et al., 2008). In people with impaired CA,

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