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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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such as patients with stroke, Mx is higher than that in healthy people (Reinhard et al., 2005; Reinhard et al., 2008), and the phase shift at LF between the cerebral BFV and BP is lower than that in healthy people (Petersen et al., 2015; Reinhard et al., 2008).

2.3. Statistical analysis

Nonparametric statistical analysis was applied because of the nonnormal distribution of the data. We compared continuous and categorical variables between the patients and healthy controls by using the Mann–Whitney *U* test and Fisher's exact test, respectively. The correlation between the variables was tested using Spearman's rank correlation coefficient. The data were expressed as the median and interquartile range (IQR), and $p < 0.05$ was considered statistically significant. Statistical data were analyzed using PASW Statistics for Windows version 18.0 (SPSS Inc., Chicago, IL, USA) and MedCalc Statistical Software version 16.8 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016).

3. Results

The characteristics of the participants are listed in Table 1. In this study, 21 patients with schizophrenia (median age = 42 years, six males) and 23 healthy controls (median age = 42 years, five males) were analyzed. None of the participants had a history of cardiovascular diseases, hypertension, or diabetes mellitus. The patients and controls did not differ in age, sex, body mass index (BMI), and tobacco smoking habits. The median duration of illness in the patients with schizophrenia was 9 years (IQR: 5–20 years) and the median PANSS score was 67 (IQR: 63–79). At the time of the study, all patients received stable doses of antipsychotics [median chlorpromazine (CPZ) equivalent = 563 mg/day, IQR: 375–731 mg/day].

A comparison of CA indices between the patients with schizophrenia and controls is presented in Fig. 1 and Supplementary Table 2. Mx in the patients was significantly higher than that in the controls (0.399 vs. 0.257, $p = 0.036$, Fig. 1A). TFA revealed that the phase shift at LF in the patients was significantly lower than that in the controls (38.7° vs. 44.3°, $p = 0.019$, Fig. 1B), and the phase shift at VLF in the patients was lower than that in the controls, but the difference was borderline significant (57.2° vs. 66.6°, $p = 0.076$, Fig. 1B). The phase shift at HF (Fig. 1B) and gains at all frequency bands (Fig. 1C) did not differ significantly between the patients and controls. The Mx, phase shift at all frequency bands, and gain at all frequency bands in the patients did not significantly correlate with the PANSS score or its subdomains, duration of illness, CPZ equivalents of antipsychotics, and BMI ($p > 0.05$ for Spearman's rank correlation coefficient, data not shown).

4. Discussion

The poorer Mx and phase shift in the patients with schizophrenia compared with the controls indicated the impaired maintenance of constant CBF and a delayed cerebrovascular autoregulatory response; however, none of the patients had a history of cerebrovascular disease, hypertension, or diabetes. Therefore, the impaired CA of the patients could not be explained by the presence of a preexisting cerebrovascular disease. Furthermore, the CA indices of the patients did not correlate with the CPZ equivalents, PANSS score, or duration of illness. To our knowledge, this is the first study to report impaired CA in patients with schizophrenia.

The median value of Mx in our controls (0.257) was consistent with those reported by Reinhard et al. (2005) and Reinhard et al. (2008) (Mx = 0.20 and 0.28, respectively) in controls. The median value of the phase shift in our controls (44.3° at LF) was consistent with those in controls reported by Petersen et al. (2015) (47° at LF), Reinhard et al. (2005) (48° at LF), and Reinhard et al. (2008) (40° at LF). The median value of Mx in our patients with schizophrenia (0.399) was higher than that in patients with stroke reported by Reinhard et al. (2005) (Mx = 0.27). The median value of phase shift in our patients with schizophrenia (38.7° at LF) was consistent with those of patients with stroke reported by Petersen et al. (2015) (29.6° at LF) and Reinhard et al. (2005) (39° at LF). Therefore, the alterations of CA indices in patients with schizophrenia are comparable with those in patients with cerebrovascular diseases.

The mechanism of CA is complex and incompletely understood, but CA has been proposed to control CBF by adjusting the vascular resistance of cerebral small vessels through myogenic, neurogenic, and metabolic mechanisms (Cipolla, 2009; van Beek et al., 2008). Vascular endothelial derived nitric oxide (NO) is responsible for vasodilation, which reduces the vascular resistance and increases CBF (Cipolla, 2009; Toda et al., 2009). Inhibition of NO synthase resulted in CA impairment in a study on human participants (White et al., 2000); therefore, the production of NO affects CA. NO and its related biochemical pathways are associated with the pathogenesis of schizophrenia through oxidative stress and disturbances in neurodevelopment (Nasyrova et al., 2015). Compared with healthy controls, the plasma NO levels were lower in patients with schizophrenia before antipsychotic treatment (Lee and Kim, 2008; Nakano et al., 2010) and higher in patients with schizophrenia receiving antipsychotic treatment (Maia-de-Oliveira et al., 2012). An increased NO level was found in the postmortem brain tissues of patients with schizophrenia (Yao et al., 2004). Therefore, the production and metabolism of NO are disturbed in patients with schizophrenia, which may explain their impaired CA. However,

Table 1
Characteristics of the study participants.

	Controls N = 23	Patients N = 21	p Value
Median age (years)-median (IQR)	42 (32–53)	42 (36–48)	0.833
Sex: male (%)	5 (21.7%)	6 (28.6%)	0.732
Body mass index-median (IQR)	23.5 (21.0–25.4)	24.0 (22.0–28.5)	0.318
Hypertension (%)	0 (0%)	0 (0%)	(N.A.)
Diabetes mellitus (%)	0 (0%)	0 (0%)	(N.A.)
Tobacco smoking habit (%)	1 (4%)	3 (14%)	0.335
Duration of illness (years)-median (IQR)	(N.A.)	9 (5–20)	(N.A.)
PANSS-median (IQR)	(N.A.)	67 (63–79)	(N.A.)
CPZ equivalents-median (IQR)	(N.A.)	563 (375–731)	(N.A.)
Mean arterial pressure (mmHg)-median (IQR)	82 (66–93)	83 (73–91)	0.622
Cerebral blood flow velocity (cm/s)-median (IQR)	39 (36–43)	39 (32–43)	0.733
End-tidal carbon dioxide (mmHg)-median (IQR)	37 (35–40)	36 (35–39)	0.421

IQR = interquartile range, PANSS = Positive and Negative Syndrome Scale, CPZ = chlorpromazine.
N.A. = not applicable.

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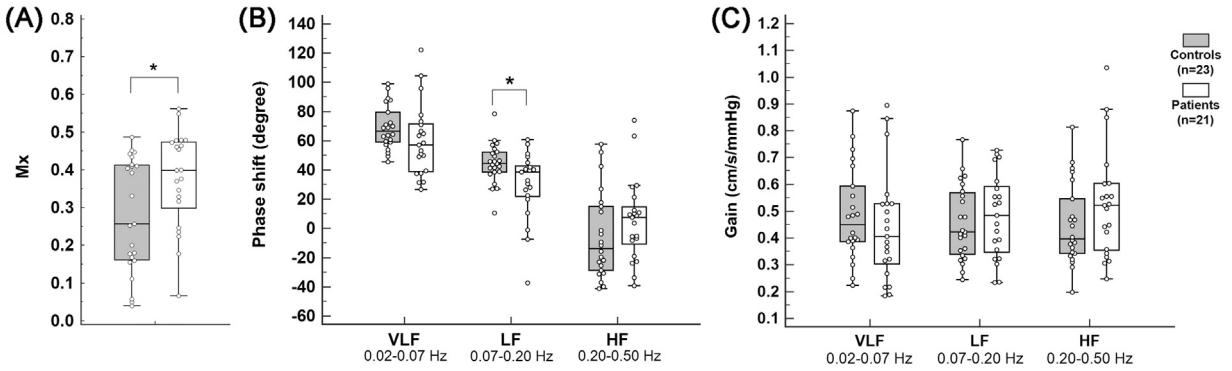

Fig. 1. Box and whisker with dot plots of cerebral autoregulation indices of the controls and schizophrenic patients: (A) Mx, (B) phase shift, (C) gain. *$p < 0.05$ between the two groups. VLF: very low frequency, LF: low frequency, HF: high frequency.

determining whether the disturbances in NO levels are the cause or consequence of schizophrenia requires further investigation.

Considering that the use of antipsychotics would increase the level of NO, the use of antipsychotics possibly alters CA. However, in the current study, the CA indices, which were impaired in the patients with schizophrenia, including Mx and the phase shift at VLF and LF, were not correlated with the CPZ equivalents. Differences in the effects of antipsychotics on CA may explain the absence of the correlation. Therefore, CPZ equivalents cannot be used as surrogates for estimating the correlation of antipsychotics with CA. Furthermore, CA involves a complex mechanism. The effect of an increased NO level on CA thus far is not clear, and antipsychotics may affect CA through other biochemical pathways. To our knowledge, no study has addressed the effect of antipsychotics on CA. In the current study, the possibility that the impaired CA in patients with schizophrenia resulted from the use of antipsychotics could not be excluded. Nevertheless, because CA correlated with neither CPZ equivalents nor the duration of illness (therefore the duration of antipsychotics use), the impaired CA cannot be explained only by the use of antipsychotics.

Inadequate CBF has been reported in many brain regions of patients with schizophrenia (Andreasen et al., 1997; Kanahara et al., 2013; Zhu et al., 2015). Inadequate CBF could be interpreted as an inadequate metabolic demand of specific neural networks or impaired CA of specific regions; however, in the current study, distinguishing between these two conditions was not possible. A study involving the induction of changes in BP and recording of task-based functional brain images may answer this question. In the current study, we assessed CA by measuring the BFV of the ICA, which represented the CBF of the entire forebrain and not of a specific region; however, a severe CA impairment of a specific brain region could affect the CA indices calculated from the CBF of the entire forebrain. Therefore, whether the impaired CA is a regional or general disturbance in the forebrain could not be answered by this study. Further investigation of the spatial distribution of CA impairment in schizophrenia may provide not only answers to the aforementioned questions but also clues regarding the pathomechanism.

Evidence supports the role of vascular disorder in schizophrenia. Patients with schizophrenia had wide retinal venules before exposure to antipsychotics, and these results were consistent in two cohorts (Meier et al., 2015; Meier et al., 2013). Wide retinal venules were also present in the healthy co-twins of patients with schizophrenia (Meier et al., 2015), implying that the vascular disorder is a genetic disorder manifesting before the onset of schizophrenic symptoms and is not a consequence of schizophrenia or medical treatment. Retinal vessels originate from the central nervous system and reflect the condition of cerebral microvessels. Wide retinal venules are associated with inflammation, atherosclerosis, cerebral small vessel disease, and the onset of cerebrovascular diseases (Cheung et al., 2013; Ikram et al., 2006; McGeechan et al., 2009). A functional genomics study involving genome-wide association revealed that the expression of several genes involved in vasoregulation, shear stress-induced endothelial function, cerebral ischemia, postischemic repair, and neurodevelopment was altered in schizophrenia (Moises et al., 2015). This indicates that vascular disorder, particularly microvascular dysfunction, is present in schizophrenia (Gutterman et al., 2016; Moises et al., 2015); however, whether this vascular disorder contributes to the pathomechanism of psychiatric symptoms remains unclear. Furthermore, whether the severity of psychiatric symptoms is associated with the severity of vascular disorders remains unclear. In this study, the PANSS score and its subdomains were not associated with CA indices. However, the small intragroup variation of disease severity in patients explains this finding. The IQR of the PANSS scores of our patients was 63–79; therefore, most of our patients were homogeneously "moderately ill" (Leucht et al., 2005). Finding a significant correlation between parameters with small variations is difficult in a small sample. A more reliable method to find the correlation between CA and symptoms is to enroll patients with different severities. Nevertheless, impaired CA and an increased risk of cerebrovascular diseases could be expected in patients with schizophrenia according to emerging evidence of vascular dysfunction in them.

This study has some limitations. First, the sample size was relatively small; however, the patients and controls did not differ in age, sex, and vascular comorbidities. Therefore, we could compare CA between the patients and controls with a small sample size and without known confounding factors. A larger sample size will be required to precisely analyze the correlation between CA and coexisting factors, such as comorbidities or medications. Second, we could not exclude the effects of antipsychotics on CA in this study. However, for confirming the effects of antipsychotics on CA, recruiting drug-naive patients with schizophrenia and observing the CA before and after using antipsychotics are necessary. However, such a study would be difficult in practice. Third, most of our patients had moderately severe symptoms. In a relatively small sample with similar disease severity, the generalizability of the study conclusions is limited and requires more investigation. Fourth, we did not record the waist circumference, lipid levels, and fasting glucose of the participants on the day of the CA test, and whether these factors differed between the patients and controls is not clear. Nevertheless, the BMIs did not differ between the patients and controls, and none of the participants had diabetes. The lipid profiles have not been found to affect CA. Therefore, the lack of these data may not appreciably affect our conclusions.

In conclusion, we found the impaired maintenance of constant CBF and a delayed cerebrovascular autoregulatory response in patients with schizophrenia. The impaired CA may be caused by schizophrenia and may not be an artifact of coexisting medical conditions. The mechanism of impaired CA in schizophrenia requires further investigation, and it may play a role in not only the development of cerebrovascular diseases but also the pathomechanism of schizophrenia.

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Contributors

HL Ku and NF Chi were responsible for study design.

HL Ku, JK Wang, HC Lee, IC Liu, YC Chen, YT Lee, IC Lin, and CP Lin were responsible for recruitment and assessment of the subjects.

HL Ku and NF Chi were responsible for cerebral autoregulation test.

HL Ku, HC Lee, TJ Lane, CJ Hu, and NF Chi were responsible for data analysis.

All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors report no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2017.01.015.

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