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Assessment of arterial stiffness among schizophrenia-spectrum disorders using aortic pulse wave velocity and arterial compliance: A pilot study

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ABSTRACT

Cardiovascular disease (CVD) is the leading cause of death in individuals with chronic schizophrenia. Arterial stiffness provides a non-invasive indication of cardiovascular disease risk. To date, arterial stiffness, which has been shown to have independent predictive value for CVD morbidity and mortality, has not been evaluated in this population. We aimed to examine aortic pulse wave velocity (aPWV) as well as large and small artery compliance (Comp1 and Comp2) in patients being treated for schizophrenia, compared to healthy volunteers. Ten patients and 10 age and gendermatched volunteers underwent a comprehensive evaluation of arterial stiffness including: aPWV, Comp1, Comp2, stroke volume, cardiac output, and systemic vascular resistance. Patient aPWV was significantly elevated compared to healthy volunteers (9.1 ± 4.11 vs. 5.7 ± 1.4, $P=0.03$). Increased age, blood pressure, heart rate, and cigarettes/day were associated with reduced arterial health in patients. This is the first time aPWV has been described in those treated for schizophrenia. Arterial stiffness is increased in this population. Measuring arterial stiffness is a non-invasive, sensitive and effective tool for evaluating CVD risk in this population.

1. Introduction

In the preceding decade cardiovascular disease (CVD) has emerged as a central underlying cause of reduced life span in patients with schizophrenia (Fleischhacker et al., 2008; Hert et al., 2009; Leucht et al., 2007) with coronary artery disease now recognized as a more prevalent cause of death than suicide in this population (Hennekens et al., 2005). Persons with schizophrenia have a two-fold increase of CVD related mortality risk as compared to controls, having increased obesity and other metabolic syndrome risk factors (Brown, 1997; Capasso et al., 2008). While some of the increased cardiovascular burden is partially attributed to newer generation antipsychotic medications (Raja, 2011), recent meta-analyses of genome wide association studies have identified a number of loci or single nucleotide polymorphisms that are highly pleiotropic with schizophrenia and cardiovascular disk risk factors (i.e., diabetes, obesity, reduced high-density and elevated low-density cholesterol, diastolic blood pressure) (Andreassen et al., 2013). This findings suggest that co-morbidity of CVD and schizophrenia is partially genetically modulated.

At present, efficacious management of CVD risk has not been optimized in this population, perhaps due to insufficient recognition by health professionals and/or insufficient methodologies for accurate assessment of CVD in this population. Currently, a number of consensus panels have recommended monitoring of cardio-metabolic risk factors in patients receiving the newer second generation antipsychotics. The current standard recommendations include assessment of family history, body mass index (BMI), waist circumference, blood pressure, fasting plasma glucose and lipid profile at the time of antipsychotic treatment initiation, and at regular intervals henceforth (Newcomer, 2007). These recommendations do not include an assessment of arterial stiffness, a known marker of increased CVD risk (Vlachopoulos et al., 2010). Prior studies have examined microvessel vascular reactivity in schizophrenia as a CVD risk factor, however, this measure was

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not related to CVD or CVD risk (Israel et al., 2011; Seeck et al., 2011). In contrast, measures of central arterial stiffness have recently become key clinical indicators of arteriosclerotic progression in a variety of populations (Cavalcante et al., 2011; Phillips et al., 2012a, 2012b; Vlachopoulos et al., 2010). Specifically, central pulse wave velocity (PWV) and small artery compliance have powerful predictive value for CVD mortality and morbidity (Duprez et al., 2011; Grey et al., 2003). A one-metre per second increase in central PWV is related to a 14–15% age, sex and risk-factor corrected increase in risk for cardiovascular events and CVD mortality (Vlachopoulos et al., 2010). Furthermore, a risk-factor corrected 0.71 increase in the hazard ratio for future CVD results from every standard deviation increase based on published normative data (Duprez et al., 2011).

The addition of an assessment of central arterial stiffness may provide a more accurate and more straightforward probe of CVD risk in schizophrenia. Clinically, central arterial stiffness measures CVD risk, which is not encapsulated by current established risk factors, or even the Framingham score (Mitchell et al., 2004; Newcomer, 2007). It has been demonstrated that cardiovascular risk scores predict cardiovascular mortality in clinically treated individuals with schizophrenia (Correll et al., 2006). However, CVD predictions based on traditional scoring likely underestimate or fail to estimate the true CVD risk in this population (Correll et al., 2006). In contrast, although aPWV independently predicts CVD outcome, a recent systematic review found no relationship between aPWV and traditional risk factors for CVD (Cecelja and Chowienczyk, 2009). This suggests that aPWV is related to the progression of arteriosclerosis that is not represented by traditional risk factors. Further, in healthy individuals, only 17% of the variability in aPWV is related to variability in Framingham risk-scores (Song et al., 2009).

Given the clear increase in CVD risk in this population, we posited that physiological markers of arteriosclerotic progression are central to optimal monitoring and evaluation of increased CVD risk in schizophrenia. One previous study of PWV failed to demonstrate changes in PWV in schizophrenia patients; however because this study measured the pulse transit time between the brachial and ankle regions, this assessment included both central (i.e., highly related to CVD risk) and peripheral components (i.e., doubtful association with CVD risk), and likely resulted in an inaccurate measure of CVD risk (Bar et al., 2007; Tsuchikura et al., 2010). We comprehensively and accurately evaluate arterial stiffness using central PWV as well as large and small arterial compliance in a pilot study of chronic schizophrenia patients. Schizophrenia patients were expected to have elevated aPWV scores compared to age and gender matched healthy volunteers.

2. Methods

2.1. Subjects

Subjects for this study were hospitalized chronic psychosis patients who had been recruited as part of a longitudinal pilot study on the effects of exercise on symptom severity. As part of their baseline assessment, measures of arterial stiffness were ascertained. Ethics approval for the study was provided by the University of British Columbia Clinical Research Ethics Board in accordance with Tri-council Policy. All participants provided full written informed consent. Inclusion criteria were as follows: age 18–55 years, current DSM-IV diagnosis of schizophrenia or schizoaffective disorder, ability to provide full written consent, IQ of 75 or greater, normal visual acuity with or without correction (glasses, contact lenses), and fluency in English. Exclusionary criteria were: a history of significant head injury (unconsciousness for greater than 5 min), a history of substance dependence in the previous 6 months, a history of physical disability precluding normal range of motion or prosthetic limb, a history of significant cardiovascular disease contra-indicating regular physical exertion (physician determined). All antipsychotic and adjunct medication treatments for these patients were determined by their clinicians (see Table 1). Ten individuals who met DSM-IV criteria for schizophrenia ($n=1$) or schizoeffective ($n=9$) disorder participated in this study (Patients). All diagnostic evaluations were performed by consensus diagnosis by trained clinicians (SWF, DF). The healthy volunteer group was comprised of 10 participants matched for age and sex (Controls). Participants from the patient group were inpatients from the BC Psychosis Ward, a 25-bed unit mandated to treat refractory psychosis patients. Symptom severity was rated with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Depressive symptoms over the past two weeks were quantified using the Calgary Depression Scale (CDS) (Addington et al., 1992). Both PANSS and CDS were performed by a trained clinician (SWF). The antipsychotic medications prescribed at baseline included aripripazole, clozapine, olanzapine, flupenthixol, risperidone, palliperidone and loxapine. The mean chlorpromazine dose equivalent was 307 ± 12 CPZ/day. Standard doses are shown in Table 1.

Table 1
Demographic Data and Medications (note: 60% of patients are receiving polypharmacy antipsychotic treatment at entry).

Variable	Controls	Patients
Age, years (mean, S.D., range)	28 (7), 22–40	28 (5), 21–40
Gender (*N*)		
Male	5	5
Female	5	5
Duration of Illness (years)	N/A	19.9 (5.8), 7–16
Yrs Education	13.5 (1.4), 12–15	11.1 (2.0), 8–15
Ethnicity (*N*)		
Caucasian	7	7
Asian	2	0
Aboriginal	1	2
Other	0	1
Baseline Antipsychotic-Dose Range (mg/d)		
Aripriprazole ($N=4$)	N/A	15–25
Clozapine ($N=5$)		175–375
Olanzapine ($N=1$)		10
Quetiapine ($N=1$)		900
Paliperidone inj ($N=2$)		100–150
Loxapine ($N=1$)		80
Flupentixol ($N=1$)		100
Risperidone LA Q2w ($N=1$)		25
Baseline Adjunct Medications		Fluoxetine Lithium Benztropine Clonazepam Buproprion Escitalipram

Both antiadrenergic ($HAL\alpha_1$) and anticholinergic load ($BENZ_{ChR}$) were calculated as previously described (Minzenberg and Yoon, 2011; Minzenberg et al., 2004) based on medications that the patients were administered the day of cardiovascular assessment. Control participants were recruited from posters placed around the University of British Columbia campus. Participant characteristics are presented in Table 1. All participants (Patients and Controls) were tested in the morning approximately 90 min following a light breakfast. Smoking in patient group was allowed (a maximum of one cigarette 45–60 min before cardiovascular assessments). No patients or controls were being treated for diabetes. Ward physicians confirmed the absence of diabetes in all patients enrolled in this study. Additional confirmatory laboratory measures of blood glucose were not available at the time of the study. All patients had abstained from alcohol for at least 1 month before this study.

2.2. Arterial stiffness measures

A comprehensive arterial evaluation measuring both arterial compliance and aPWV, as described in our previous work, required approximately 60 min of supine rest in a quiet laboratory (Phillips et al., 2012a). Briefly, participants were first positioned supine on a dedicated research bed. Blood pressure (BP) was measured six repeated times (separated by one minute) using a validated automated cuff (such as BpTRU-BPM-100, Coquitlam, VSM Medical, Vancouver, BC, Canada) after 5 min of supine rest. The latter five BP and heart rate measures separated by at least 1 min were averaged for a final score. Mean arterial pressure (MAP) was calculated as [2*Diastolic Blood Pressure (DBP)+Systolic Blood Pressure (SBP)]/3. Following BP measurements, arterial compliance was measured non-invasively. For measuring arterial compliance, we used applanation tonometry through the HDI CR-2000 (Hypertension Diagnostics, Eagan, Minnesota), which employed a diastolic pulse contour analysis. This model considers the arterial tree loaded by stroke volume