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Peripheral endothelial dysfunction as a marker of cardiovascular risk in physically healthy patients with schizophrenia and related psychoses: A matched case control study

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Abstract

OBJECTIVES: Our aim was to assess endothelial function in physically healthy patients with schizophrenia and related psychoses and to compare the results with healthy controls. Endothelial dysfunction was shown to predict future cardiovascular events in general population so we assumed to find a higher prevalence of endothelial dysfunction in patients with psychosis, as their cardiovascular morbidity is markedly higher than in general population, and to confirm the referred correlation with the traditional cardiovascular (CV) risk factors.

DESIGN: We assessed the traditional CV risk factors and endothelial function using non-invasive peripheral arterial tonometry (EndoPAT2000) in 50 stabilized and medicated schizophrenic patients (aged between 18 and 50 years) without any history of cardiovascular diseases and compared the results with 50 age-matched healthy controls.

SETTING: Psychiatric Clinic, University Hospital, Hradec Kralove and 2nd Department of Internal Medicine, General University Hospital, Prague, Czech Republic

RESULTS: There was no difference in relative hyperaemia index as an endothelial function measure between patients and controls (2.19±0.68 vs. 1.98±0.57, p=NS) and there were also no correlations between reactive hyperaemia index and the traditional CV risk factors, illness duration or psychotic symptoms. On the other hand, the two study groups differed significantly in almost all traditional CV risk factors.

ORIGINAL ARTICLE

CONCLUSIONS: The absence of different prevalence of endothelial dysfunction together with clearly different cardiovascular risk factors profile observed in our patients with psychosis and matched healthy controls raise questions about the disparities in applicability of different markers or methods of cardiovascular risk assessment in patients with schizophrenia and general population.

Abbreviations:

BMI	- body mass index
CGI	- Clinical Global Impression
CV	- cardiovascular
DBP	- diastolic blood pressure
ED	- endothelial dysfunction
FMD	- flow mediated dilatation
HDL	- high density lipoprotein
ICD-10	- 10th revision of the International Statistical Classification of Diseases and Related Health Problems
LDL	- low density lipoprotein
NCEP/ATP III	- National Cholesterol Education Program/Adult Treatment Panel III
PANSS	- Positive and Negative Syndrome Scale
PAT	- peripheral arterial tonometry
RHI	- relative hyperaemia index
RH-PAT	- reactive hyperaemia-peripheral arterial tonometry
SBP	- systolic blood pressure
SD	- standard deviation

INTRODUCTION

Patients suffering from schizophrenia are known to have eleven to twenty years lower average life expectancy compared to general population (Newcomer, 2007; Tenback *et al.* 2012; Nielsen *et al.* 2013). Moreover, the difference in life expectancy has become even larger in last decades (Weinmann *et al.* 2009; Nielsen *et al.* 2013). As expected, a higher suicide rate participates on increased mortality in schizophrenia patients. Nevertheless, a contribution of cardiovascular (CV) diseases to premature mortality in schizophrenia has been increasingly recognised since the prevalence of CV diseases has been reported to be twice higher than in general population. (Osby *et al.* 2000; Curkendall *et al.* 2004; Leucht *et al.* 2007; Tiihonen *et al.* 2009; De Hert *et al.* 2011). A relatively high prevalence of CV diseases and its contribution to lower quality of life, increased costs and overall premature mortality of schizophrenia patients warrants early diagnosis and identification of markers or risk factors that could help in early interventions in this patient population. Patients with schizophrenia have increased prevalence of traditional CV risk factors including hyperglycaemia, dyslipidaemia, obesity, hypertension and smoking (Bernando *et al.* 2009; De Hert *et al.* 2010). However, traditional CV risk factors as well as their combination may fail to predict the development of coronary heart disease and other serious cardiovascular events in 25 to 50% of cases in general population (Reriani *et al.* 2010; Perk *et al.* 2012; Blum & Nahir, 2013). Thus, their predictive value in patients with schizophrenia is likely to be limited too.

All these traditional CV risk factors either directly or indirectly participate on an endothelial dysfunction (ED) which is a widely recognised prerequisite of atherosclerosis development and in turn a direct precursor of symptomatic CV disease. Endothelial function has been shown to be impaired in patients with hypertension, type II diabetes mellitus, obesity, renal failure, hypercholesterolemia as well as coronary artery disease (Bonetti *et al.* 2003; Moerland *et al.* 2012; Blum & Nahir, 2013). Viewing ED as a result of CV risk factors and susceptibility of individual patients to these factors given by their genetic predisposition, local factors and other yet-unknown factors, an evaluation of ED could serve as a potentially better predictor of development of CV diseases (Bonetti *et al.* 2003; Reriani *et al.* 2011). Apart from invasive, costly and thus not widely used approaches, as the measurement of acetylcholine-induced changes in coronary blood flow, ED can be assessed non-invasively. The brachial artery flow-mediated dilation capability (FMD) is the most commonly used non-invasive technique for investigation of endothelial function. FMD involves ultrasound measurement of the change of diameter of the brachial artery in response to increased flow, typically induced by a period of ischemia in the forearm arteries. Nevertheless, significant intra and inter-observer variation and the absence of correction for changes in systemic hemodynamics limit its use (Reriani *et al.* 2011; Poredos & Jezovnik, 2013).

Reactive hyperaemia-peripheral arterial tonometry (RH-PAT) is a novel, non-invasive, investigator-independent and easy to use technique for assessment of peripheral ED that has been recently validated (Axtell *et al.* 2010; Reriani *et al.* 2011) and correlated well with invasive (Bonetti *et al.* 2004) as well as with non-invasive methods of ED evaluation (Kuvin *et al.* 2003). Moreover, a prospective study with 7-year follow up found relative hyperemia index (RHI) as an ED measure to be an independent predictor of adverse CV events in 270 outpatients with intermediate CV risk (Rubinshtein *et al.* 2010).

Interestingly, the research regarding CV morbidity in patients with schizophrenia has focused mainly on metabolic syndrome and CV risk factors with only sparse information about peripheral vasculature in the disease (Israel *et al.* 2011). So far, there has been only one published study using RH-PAT in 83, middle-aged patients with schizophrenia that focused on the association of dietary and pharmacogenetic factors with the endothelial function (Ellingrod *et al.* 2011).

Our aim was to validate the hypothesis that endothelial function assessed by RH-PAT would serve as a sensitive marker for screening of relatively young patients with schizophrenia with no cardiovascular disease present or in personal history to select the individuals with a high risk of future CV morbidity and/or fatal CV events.

MATERIAL AND METHODS

Subjects

Fifty patients with schizophrenia and related psychoses treated in an outpatient psychiatric clinic were enrolled in the study after meeting following inclusion and exclusion criteria. The control group consisted of healthy age- and sex-matched volunteers. The control group was recruited from medical staff, their family members or friends. Informed consent was obtained from all subjects prior the study. The study was approved by the local ethics committee and complies with the Declaration of Helsinki.

Inclusion criteria were as follows: 1) the patients were diagnosed with schizophrenia, schizoaffective disorder or acute psychotic disorder according to ICD-10 criteria, 2) age between 18 and 50 years, 3) remission of psychotic disorder according to Andreasen criteria (Positive and Negative Syndrome Scale [PANSS] items P1, P2, P3, N1, N4, N6, G5, G9 ≤3 points for the last six months), 4) patients were stable on antipsychotic medication for the last 3 months. The exclusion criteria included any known cardiovascular or metabolic disorder (either present or documented in the personal history) and current substance abuse diagnosis. The patients in remission of psychotic disorder were chosen to prevent the acute stress-related endocrine changes to interfere with the results.

Procedures

After meeting the inclusion and exclusion criteria, all patients were examined in the morning between 8 a.m. and noon after at least 8 hours of fasting and not smoking. The family history of cardiovascular disease, personal history, smoking status, current alcohol and drug abuse were obtained and patients with psychosis underwent a clinical interview with trained psychiatrist that included PANSS and Clinical Global Impression (CGI). The blood pressure, weight, height (to calculate the body mass index [BMI]), and the waist circumference were measured in all study participants and blood samples were drawn for the analysis of following fasting laboratory parameters: total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL) and glycaemia. The cut-off values of cardiovascular risk factors were adopted from National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III) (Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults, 2001) and were following: fasting glucose >7.0 mmol/l, fasting total cholesterol >5.17 mmol/l, HDL <1.03 mmol/l, LDL ≥3.36 mmol/l, systolic blood pressure (SBP) ≥130 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, waist circumference >102 (men) and >88 (women), and BMI ≥25.

Endothelial function assessment

Peripheral endothelial function was assessed at standard conditions (all subjects remaining fasting and not smoking) at the same time of the day. Previously validated device EndoPAT 2000 (Itamar Medical Ltd; Caesarea, Israel) has been used for measurements. EndoPAT enables non-invasive plethysmographic recording of finger arterial pulse wave amplitude, which is a measure of pulsatile volume changes. The pulse wave amplitude is assessed before and after reactive hyperaemia. Its detailed mechanism of action was described elsewhere (Axtell *et al.* 2010). Briefly, Two finger probes are placed on the subject's middle finger of each hand. The probes are inflated to allow pulse wave measurement and the subject is then asked to stay motionless for 15 minutes. The baseline measurement is performed for 5 minutes then the blood pressure cuff located on subject's non-dominate arm is inflated to 60 mmHg above baseline systolic pressure or to minimum 200 mmHg pressure. After 5-minute occlusion, the cuff is rapidly deflated and the post-deflation measurement is done for 5 minutes. Relative hyperaemia index (RHI) is calculated automatically as a difference between baseline and post-deflation measurement. The final RHI is normalized for baseline signal and indexed to the contra-lateral arm. The threshold of RHI <1.67 (based on comparison with the "gold standard" invasive measurement of endothelial dysfunction) has been set by Itamar company for clinical use, and has been used for ED identification in majority of studies (Bonetti *et al.* 2004).

Statistical analysis

Shapiro-Wilk test was used to assess normality. Non-parametric tests were used in the analysis since majority of continuous data were non-normally distributed. Continuous data were summarized using median with 25^{th} and 75^{th} percentile or mean ± standard deviation (SD), as appropriate, and differences between patients and controls were compared using Mann Whitney U. Proportions were summarized using percentages and compared with the Pearson Chi-square test. Spearman Correlation Coefficient was used to evaluate relation of continuous variables with RHI in both groups. A value of $p<0.05$ was considered significant.

RESULTS

Out of 129 patients screened between May and December 2011, fifty patients fulfilled inclusion and exclusion criteria. Out of those, 70% were diagnosed with schizophrenia, 24% with schizoaffective disorder and 6% with an acute psychotic disorder according to ICD-10 criteria. The average duration of the disease was 10±7 years. All patients were treated with antipsychotic drugs; 60% received monotherapy with atypical antipsychotic agent, 6% were on monotherapy with classic antipsychotic drug and 36% received a combination of two antipsychotics. Fifty healthy age- and sex-matched subjects were used as a control group for further analysis. All study participants reported to be Caucasians.

The mean age of both study groups was 34±7 years and there were 72% males.

The prevalence and nominal values of individual cardiovascular risk factors of patient and control groups are presented in Table 1. Patients had significantly higher glycaemia, total cholesterol, HDL, LDL, waist circumference and BMI compared to control group. There was no difference either in systolic or diastolic blood pressure.

There was no significant difference between patient and control group in RH-PAT index in values 2.19±0.68 vs. 1.98±0.57 (p=0.16) or prevalence of ED (defined as RH-PAT index <1.67) 30% vs. 28% (p=0.83). There were significantly more smokers in the patient group compared to controls (52% vs 12%, p<0.001).

Except for diastolic blood pressure in patient group and total population, there was no correlation (Table 2) between RH-PAT index and other cardiovascular risk factors (including glycemia, total cholesterol, LDL, HDL, waist circumference or BMI). RH-PAT index did not correlate with PANSS or disease duration either.

Tab. 1. Comparison of cardiovascular risk factors prevalence and values in patient and control groups.

Cardiovascular risk factor	Patient Group n=50	Control Group n=50	*p*-value
Glycemia (mmol/l)	5.0 [4.8–5.3]	4.6 [4.4–5.0]	<0.001
>7 mmol/l (n)	0 (0%)	0 (0%)	
Total cholesterol (mmol/l)	5.04 [4.46–5.99]	4.61 [4.06–5.20]	0.009
>5.17 mmol/l (n)	23 (46%)	14 (28%)	
HDL (mmol/l)	1.24 [1.03–1.39]	1.40 [1.24–1.70]	0.001
<1.03 mmol/l (n)	13 (26%)	4 (8%)	
LDL (mmol/l)	3.46 [2.94–4.26]	2.65 [2.10–3.07]	<0.001
≥3.36 mmol/l (n)	28 (56%)	7 (14%)	
SBP (mmHg)	125 [110–130]	120 [110–130]	0.649
≥140 mmHg (n)	6 (12%)	7 (14%)	
DBP* (mmHg)	70 [65–80]	70 [60–80]	0.094
≥90 mmHg (n)	2 (4%)	1 (2%)	
Waist circumference (cm)	99 [94–107]	84 [75–90]	<0.001
>102cm or >88 cm* (n)	23 (46%)	5 (10%)	
BMI (kg/m^2)	28.7 [24.9–32.1]	23.4 [22.4–25.2]	<0.001
≥25 kg/m^2 (n,%)	37 (74%)	13 (27%)	

Continuous variables are expressed as median [25th–75th percentile]. Cutoffs of cardiovascular risk factors are based on National Cholesterol Education Program / Adult Treatment Panel III; HDL = high density lipoprotein, LDL = low density lipoprotein; SBP = systolic blood pressure; DBP = diastolic blood pressure; BMI = body mass index. * cutoff 102 cm is applicable to men and 88 cm to women

DISCUSSION

In the presented investigation, 30% of patients with schizophrenia and related psychoses met the criteria for endothelial dysfunction (RH-PAT<1.67). One could consider that proportion as high in such a young population and comparable to 50% in older (45.89±111.49 vs 34±7 years in our study group) population of schizophrenia patients with more pronounced CV risk factor burden (Ellingrod *et al.* 2011). However, when compared with matched control group, no significant differences were found regarding endothelial function. The comparison of such result with the relevant data by Ellingrod *et al.* (2011) was not possible, as the study didn't include a control group. Endothelial dysfunction was described as the sum of cardiovascular risk factor burden plus all vasculoprotective factors of an individual (Reriani *et al.* 2010) but our two study groups significantly differed in almost all CV risk factors while having very similar state of endothelial function. We could only hypothesize, whether such discrepancy is the matter of the test we have chosen to measure the endothelial function, the timing of the examination, or whether there is a different mechanism leading to increased CV morbidity in patients with schizophrenia.

EndoPAT 2000 has been used to assess endothelial dysfunction in general population with promising results (Bonetti *et al.* 2004; Hamburg *et al.* 2008; Rubinsthein *et al.* 2010; Toggweiler *et al.* 2010). A study with endothelial nitric oxide inhibitor showed that approximately one half of an increase of the digital pulse volume amplitude is mediated by nitric oxide (Nohria *et al.* 2006), and as such the nitric oxide plays an important role both in digital peripheral arterial tonometry (PAT) and FMD. However, some authors question the utility of PAT measurement in CV risk prediction as it determines the endothelial function at the level of microcirculation, which is distinct to endothelial function of large arteries investigated by FMD (Poredos & Jezovnik 2013). A study by Moerland *et al.* (2012) supported that uncertainty, as the EndoPAT 2000 didn't detect an effect of robust interventions on endothelial function, such as smoking or glucose load, in healthy volunteers. Unfortunately, the study involved only 12 subjects (6 for each intervention) so it's not adequate to draw any firm conclusions.

In a study conducted on 1957 Framingham Third Generation cohort participants, Hamburg *et al.* (2008) found the natural logarithm of RH-PAD RHI measured by EndoPAT 2000 to be inversely related to multiple CV risk factors (BMI, total/HDL cholesterol ratio, diabetes, smoking). The only correlation found by Ellingrod *et al.* (2011) was between RHI and BMI and no such relations were observed in our study. In agreement with

Tab. 2. Correlations between RH Index and CV risk factors analysed in the total population and separately in the patient and control group.

Variable correlated with RH Index	Overall (n=100)		Control Group (n=50)		Patient group (n=50)	
	Spearman rho	*p*–value	Spearman rho	*p*–value	Spearman rho	*p*–value
Glycemia (mmol/l)	0.04	0.70	–0.02	0.90	–0.07	0.64
Total Cholesterol (mmol/l)	–0.03	0.80	–0.16	0.28	–0.03	0.84
HDL (mmol/l)	–0.02	0.86	0.13	0.37	–0.03	0.85
LDL (mmol/l)	–0.01	0.91	–0.13	0.35	–0.05	0.75
SBP (mmHg)	0.04	0.68	0.06	0.69	0.03	0.84
DBP (mmHg)	–0.23	0.02	–0.08	0.59	–0.31	0.03
Waist Circumference (cm)	0.11	0.28	0.03	0.81	0.02	0.88
BMI (kg/m^2)	0.02	0.83	–0.25	0.08	0.07	0.64

HDL = high density lipoprotein, LDL = low density lipoprotein; SBP = systolic blood pressure; DBP = diastolic blood pressure; BMI = body mass index.

our results, Ellingrod *et al.* (2011) failed to detect a correlation between RH-PAT ratio and smoking, which is a potent risk factor for endothelial dysfunction. The authors hypothesized about the possibly different nicotine metabolism in patients with schizophrenia that causes their relatively low incidence of lung cancer and might also attenuate the effect of smoking on endothelial function. Nevertheless no such plausible explanation could be found for the lack of correlation between RH-PAT ratio and other CV risk factors. Moreover, there is another study in general population that didn't find significant differences in RHI values measured by EndoPAT 2000 between subjects with different CV risk factors (Syvanen *et al.* 2011).

Possible explanation for the similar point prevalence of endothelial dysfunction in our patient and control groups might be the young age of our study participants. The mean age in crucial RH-PAT studies (Kuvin *et al.* 2003; Bonetti *et al.* 2004; Hamburg *et al.* 2008; Rubinshtein *et al.* 2010) and the study by Ellingrod *et al.* (2011) was at least ten years higher. We could theorize that the measurable effect of CV risk factors and other mechanisms on the endothelial function would develop in our study population in 5 to 10 years. Interestingly, Israel *et al.* (2011) found blunted hyperaemic response of capillary blood flow in 21 schizophrenia patients with mean age 31.8 (± 10.2) years compared to 21 matched controls. However the patients were in acute psychosis, so the impact of stress related increased sympathetic-adrenal activity couldn't be ruled out.

Recent systematic reviews and meta-analyses provided the evidence of a role of immunologic abnormalities in aetiology and pathophysiology of schizophrenia and found altered levels of cytokines, chemokines and other inflammatory substances in the peripheral blood of schizophrenic patients (Miller *et al.* 2011; Beumer *et al.* 2012; Steiner *et al.* 2014). Antipsychotic medication or other external factors can influence a certain proportion of those compounds but others are considered to be trait markers of the disease. Moreover, markers of thrombogenesis were observed to be activated in drug-naïve psychotic patients (Masopust *et al.* 2011). Considering that information, there is a possibility that the mechanisms leading to CV and metabolic diseases in patients with schizophrenia differs from the general population and that current devices assessing endothelial dysfunction, as EndoPAT 2000, might not be sensitive or specific enough to serve as a screening method for individuals with schizophrenia at risk of future CV events.

Strength and limitations

The present investigation has several limitations. Due to a cross-sectional design we weren't able to assess the capability of CV risk factors or endothelial dysfunction to predict future cardiovascular events. To at least partially overcome that limitation, the follow up checks in 5-year intervals are planned for the whole accessible study population. We acknowledge that antipsychotic medication that was present in all our patients with psychosis disturbed the clarity of the investigation as the antipsychotics interfere with the cardiovascular system as well as with the glucose and lipid metabolism (Melkersson & Dahl, 2004). On the other hand, the present medication could have worsen all the investigated parameters, including endothelial function, and as such can't explain the negative findings regarding hypothesized increased prevalence of endothelial dysfunction in schizophrenia patients. It is known that antipsychotics differ in their impact on cardiovascular or metabolic parameters according to their receptor profiles. Unfortunately, due to small number of patients medicated by the same antipsychotic, we weren't able to assess the possible effect of individual drugs on endothelial function or CV risk factors. Lastly, the sample size investigated in present study is rather small compared to cohorts examined for endothelial dysfunction in general population and consists exclusively of white

individuals of European origin, limiting the generalization of our results to the different ethnic groups.

Despite the above limitations, this study was the first to compare the peripheral endothelial function in young, medicated, physically healthy patients with schizophrenia and matched control subjects from general population. The negative outcomes of present investigation regarding the endothelial dysfunction raise important questions about the aetiology and mechanisms of increased cardiovascular morbidity in schizophrenia and the methods of detection the individuals in risk of cardiovascular diseases, and thus should be followed by further explorations.

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