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## Reduced arterial compliance in patients with psychiatric diagnoses★

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### Abstract

**Background**—Peripheral arterial compliance is a measure of elasticity of the arteries that has been found to be a robust predictor of prevalent arteriosclerosis as well as incident stroke and myocardial infarction. Psychiatric diagnoses and second generation antipsychotics may contribute to cardiovascular risk and stroke, but effects on peripheral arterial compliance are unknown. This study compared peripheral arterial compliance in healthy male controls to male patients with psychiatric diagnoses who were treated with quetiapine or risperidone or off antipsychotics at time of testing.

**Methods**—The groups consisted of 63 patients with mental illness taking quetiapine, risperidone, or no antipsychotics. There were 111 males in the control group. Mean thigh and calf arterial compliance among four groups were compared by ANCOVA, adjusting for body mass index and Framingham Risk Score. All patients were also compared to the control group. Compliance was measured with a computerized plethysmography device.

**Results**—Patients ( $n = 63$ ) had significantly lower arterial compliance in both thigh and calf than the controls. Arterial compliance in the calf was significantly lower in the subgroups of quetiapine

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**Contributors** E. Duncan and W. Brown designed the study and wrote the protocol. M. Koola, B. Cuthbert, and J. Hollis collected the data. C. Qualls performed the statistical analyses. W. Brown, N.A. Le and J. Raines provided blinded measurements in the control subjects collected as part of another study. Maju Koola wrote the first draft of the manuscript. M. Koola, E. Duncan, W. Brown, C. Qualls and D. Kelly analyzed and interpreted the results. All authors reviewed, edited, contributed to and have approved the final manuscript.

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( $n=16$ ) and risperidone ( $n=19$ ) treated, and in unmedicated ( $n=28$ ) patients than in controls. In the thigh, patients taking either quetiapine or risperidone had significantly lower arterial compliance than controls. These subgroups did not differ from each other in arterial compliance.

**Conclusion**—The presence of psychiatric diagnoses is associated with reduced arterial compliance. A large study may be required to measure any specific effects of antipsychotics such as quetiapine and risperidone on compliance compared to controls.

## Keywords

Peripheral arterial compliance; Quetiapine; Risperidone; Vasogram; Metabolic risk; Inflammation

## 1. Introduction

Treatment with second generation antipsychotics (SGAs) is associated with metabolic syndrome (Newcomer, 2007), which is associated with increased risk of myocardial infarction and stroke (Horlick, 1994). Peripheral arterial compliance (PAC) is the distensibility or elasticity of the large muscular arteries in the leg. PAC is defined as the change in volume ( $\delta V$ ) of an artery per unit change in pressure ( $\delta P$ ): Compliance =  $\delta V/\delta P$ . The Vasocor, Inc., Charleston, SC, provided the vasogram device, which has many advantages: portable office-based, non-invasive, inexpensive, automated, and completed in 15 min.

PAC is correlated with coronary artery disease and coronary angiography in 346 patients (Willens et al., 2003). Another study of 376 patients found similar results even after accounting for other cardiovascular risk factors including age, sex, diabetes, smoking, hyperlipidemia, hypertension and obesity (Herrington et al., 2003). Animal (Farrar et al., 1991) and human (Wada et al., 1994) data indicate that arterial stiffness correlates with aortic atherosclerosis at necropsy. PAC strongly predicted extensive subclinical atherosclerosis in 267 subjects (Herrington et al., 2004). The correlations between paired measurements of calf and thigh compliance values obtained during the first and second visits were 0.77 ml ( $p<0.0001$ ) and 0.79 ml ( $p<0.0001$ ), respectively (Herrington et al., 2003). Improved PAC using the vasogram has been demonstrated after aggressive cholesterol reduction (Saliashvili et al., 2004).

## 2. Research question

The specific aim of this study was to compare PAC in healthy controls (CONT) with psychiatric patients (AllPts). Subgroups of psychiatric subjects treated with either quetiapine (QUET) or risperidone (RISP) or off antipsychotics for 2 months (NOMED) were also compared. We hypothesized that AllPts, QUET and RISP subjects would have lower PAC than CONT.

## 3. Methods

### 3.1. Participants

Psychiatric subjects ( $n=63$ ) were recruited from the Atlanta Veterans Affairs Medical Center (VAMC) from August 2005 to February 2010. The QUET ( $n=16$ ) and RISP ( $n=19$ ) subjects were males of ages 18–70 years treated with oral QUET or RISP or long-acting injectable risperidone 25 mg/2 weeks ( $n=4$ ) for at least 3 months. Historical CONT ( $n=111$ ) were collected in 2004–2005 in a multisite study conducted at the University of Miami, Columbia University, Wake Forest University and Emory University (Atlanta VAMC) to test the precision of the vasogram. None had psychiatric history, and most were not VA patients (Le

et al., 2005). There were no site differences in PAC for controls in this dataset. They were age and sex matched with the psychiatric subjects. Exclusion criteria were type 1 or 2 diabetes mellitus, with weight of >300 lb, triglyceride levels of >600 mg/dl, current treatment with clozapine, a history of myocardial infarction or unstable angina within the past 6 months, diagnosed with HIV/AIDS or collagen vascular disease, current substance (except nicotine and caffeine) or alcohol abuse/dependence within 3 months prior to testing.

### 3.2. Study design

This was a cross-section between group studies to examine PAC. Changes in arterial volume in the thigh and calf across the cardiac cycle were measured using air plethysmography (Vasogram).

### 3.3. Subject assessments

Subjects signed informed consent and the Health Insurance Portability and Accountability Act forms approved by the local institutional review board and by the Atlanta VA Research and Development Committee for Emory University subjects. Socio-demographic and clinical information was collected from the subjects and electronic medical records. Height and weight were assessed at the time of vasogram. Mean arterial pressure (MAP) was computed using the formula diastolic blood pressure plus one-third pulse pressure (systolic BP–diastolic BP).

The Framingham risk score (FRS) (D'Agostino et al., 2008) provides a percentage estimate of having a major clinical coronary event during the next 10 years. It is calculated using clinical variables including age, sex, total cholesterol, high-density lipoprotein, smoker or not, on antihypertensive or not. FRS was grouped in the following categories: group 1=FRS <10%, group 2=FRS 10% and <20% and group 3=FRS 20%. In the control group, we did not have raw data for all variables that went into calculating the FRS but received the risk score already calculated for each participant. Thus, for example, we do not know how many were smokers or nonsmokers but smoking status is controlled for in the analysis.

### 3.4. Statistical analysis

The socio-demographic and clinical characteristics are represented as mean (SD) or n (%) and compared among four groups by ANOVA or Fisher's exact test as appropriate. Mean thigh and calf PAC in four groups (or between patients and control subjects) were compared by ANCOVA, adjusting for covariates body mass index (BMI) and FRS. To account for the adjustment in these analyses, PAC values are reported as least square means (LSM) and standard errors [SE]. Post hoc pairwise comparisons were done using Fisher's least significant difference method of multiple comparisons. In a post hoc power analysis, our sample sizes and an SD of 1.4 in thigh PAC in each group is adequate to detect a difference of 0.6 thigh PAC between patients and controls with 80% power and alpha=0.05. Similarly, for the calf PAC, the detectable difference is 0.35. The statistical package used was SAS 9.2. A *p* value of 0.05 was considered as statistically significant.

## 4. Results

The subjects in the psychiatric disorders group had a mixture of diagnoses as follows: schizophrenia/schizoaffective disorder (*n*=21; two had co-morbid PTSD), psychosis not otherwise specified (*n*=2), Posttraumatic stress disorder (*n*=25; 11 co-morbid depressive disorders, two with other anxiety disorders), bipolar (*n*=1), and depressive disorders (*n*=14). Demographic and clinical variables for the subject groups are summarized in Table 1. The mean (SD) dose of quetiapine and risperidone were 240.6 (173.4) and 3.8 (2.5) mg/day, respectively. Of the 28 subjects included in the NOMED group, 20 had never received a

course of treatment with any antipsychotic. Of the eight subjects with a prior history of antipsychotic treatment, their mean time since last treatment was  $1050 \pm 1413$  days.

Table 2 shows the results of PAC analyzed for differences between CONT and the psychiatric patients as a single group (AllPts). Both thigh and calf PAC were significantly lower in AllPts compared to CONT (thigh:  $F(1,169)=10.60$ ; adjusted  $p=0.001$ ; calf:  $F(1,169)=17.79$ ; adjusted  $p<0.001$ ).

Table 3 shows the results for PAC comparing CONT to the psychiatric patients analyzed as three separate medication groups. ANCOVAs for both thigh and calf PAC indicated significant differences between these four subject groups after adjusting for BMI and Framingham risk score group (thigh:  $F(3,167) = 4.15$ ; adjusted  $p = 0.007$ ; calf:  $F(3,167) = 6.32$ ; adjusted  $p < 0.001$ ).

## 5. Discussion

PAC is reduced in psychiatric patients currently treated with QUET, RISP and NOMED, compared to CONT independent of BMI and FRS.

That the NOMED group had significantly lower calf PAC than the CONT group suggests that diagnosis per se confers a risk of low PAC. It is known that risk factors for cardiovascular mortality are more common in people with mental illnesses (Newcomer, 2007), which factor may have driven our finding in the NOMED group. Thus, our findings indicate that psychiatric subjects may represent a population with lower PAC than the general population regardless of antipsychotic treatment. There is some evidence that schizophrenia in particular confers a risk of elevated glucose (Goff et al., 2005). Although not conclusively proven, low PAC in psychiatric patients may be secondary to sedentary life style, poor nutrition, smoking, metabolic syndrome and aberrant cytokines. There is a growing body of evidence showing the association of cytokine abnormalities and psychiatric disorders. However, it appears that those on QUET and RISP had the lowest PAC, suggesting that antipsychotics may be an additional risk factor for reduced PAC. The effect of SGAs on PAC has not been reported previously. This finding needs further investigation.

This study has several limitations. The small number of subjects with a diversity of psychiatric diagnoses may mask specific effects of diagnosis on PAC. Potential confounding factors such as current dose and duration of QUET and RISP were not included in the analyses. Accurate measures of outpatient adherence to QUET or RISP treatment were not assessed. Finally, CONT subjects were tested a few months before the start of data collection on psychiatric subjects, so that data collection on subject groups was not contemporaneous.

Simvastatin (40 mg/day) increased thigh compliance in all 10 patients with coronary artery disease after 2 months (Saliashvili et al., 2004).

Because of the anti-inflammatory properties of statins (Blake and Ridker, 2000; Dulak and Jozkowicz, 2005) and other medications with similar mechanism of action, a putative PAC reduction by the SGAs might be ameliorated by then current therapy. Prospective trials are needed to examine the association between obesity and nonobesity related cytokines and PAC and whether changes in PAC can be seen after improvements or changes in antipsychotic or concomitant treatments. A comparison of antipsychotics, including those with putative low liability for metabolic syndrome would be of interest. Future research should examine the effect of psychiatric diagnoses without co-morbid diagnosis in psychotropic-naïve patients and its association with PAC.

Measuring PAC using the vasogram is a novel approach to evaluating metabolic risk in psychiatric patients. PAC may be an important surrogate marker to assess subclinical atherosclerosis and the worsening of arteriosclerosis during treatment in psychiatric patients.

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**Table 1**Socio-demographic variables and clinical characteristics<sup>a</sup>.

	CONT (n=111)	AllPts <sup>b</sup> (n=63)	NOMED (n=28)	QUET (n=16)	RISP (n=19)	<u>ANOVA</u> <i>p</i> value
Age, years	53.7 (9.1)	53.9 (9.1)	53.6 (9.7)	54.8 (7.5)	53.3 (9.8)	1.00
Systolic BP, mm Hg	129 (16.9)	137 (17.1)	138.4 (19.9) <sup>d</sup>	139.8 (17.6) <sup>d</sup>	132.2 (11.3)	0.01
Diastolic BP, mm Hg	76.3 (10.3)	82.1 (17.8)	81.2 (11.8)	87.4 (29.4) <sup>d,e</sup>	78.4 (7.4)	0.009
Mean arterial pressure	93.9 (11.3)	100.4 (15.6)	100.3 (14.1)	104.9 (22.4) <sup>d,e</sup>	96.3 (7.3)	0.003
Body mass index	26.9 (4.2)	29.9 (6.0)	28.6 (6.4)	31.0 (4.5) <sup>d</sup>	30.7 (6.7) <sup>d</sup>	<0.001
<i>FRS group<sup>c</sup></i>						
FRS group 1	41 (36.9%)	29 (46%)	15 (53.6%)	4 (25%)	10 (52.6%)	0.10 <sup>f</sup>
FRS group 2	39 (35.1%)	26 (41.3%)	11 (39.3%)	8 (50%)	7 (36.8%)	
FRS group 3 (10.5%)	31 (27.9%)		8 (12.7%)	2 (7.1%)	4 (25%)	2

CONT: control group; AllPts: all psychiatric patients; NOMED: unmedicated patients;  
 QUET: patients on quetiapine; RISP: patients on risperidone; BP: blood pressure.

<sup>a</sup>Data are means (SD) except Framingham Risk Score (FRS) groups are *n* (%).

<sup>b</sup>This group is not included in the overall or pairwise comparisons.

<sup>c</sup>FRS group assigned as follows: group 1 <10%, group 2=10–20%, group 3 >20%.

<sup>d</sup>Post hoc tests: Significantly higher than CONT.

<sup>e</sup>Post hoc tests: Significantly higher than RISP.

<sup>f</sup>Fisher's exact test.

**Table 2**

Arterial compliance in psychiatric patients versus controls adjusted for body mass index and Framingham risk score.

	<b>Controls</b>	<b>All patients</b>	<b>Adjusted</b>
<i>p</i> value			
Thigh, ml	4.70 (0.13)	3.95 (0.19)	0.001
Calf, ml	2.42 (0.07)	1.89 (0.10)	<0.001

All values are represented as least square means (standard error).

CONT: controls; AHPTs: all psychiatric patients.



**Table 3**

Arterial compliance in drug groups versus controls adjusted for body mass index and Framingham risk score.

	Controls	NOMED	QUET	RISP	Adjusted
<i>p</i> value					
Thigh, ml	4.70 (0.13)	4.19 (0.27)	3.61 (0.35)**	3.88 (0.33)*	0.007
Calf, ml	2.42 (0.07)	1.92 (0.15)**	1.70 (0.20)**	1.98 (0.18)*	<0.001

All values are represented as least square means (standard error).

CONT: control group; NOMED: patients on no antipsychotic medication; QUET: patients on quetiapine; RISP: patients on risperidone.

\*  
p<0.05 compared to CONT;

\*\*  
p<0.01 compared to CONT.