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Short Communication

Impact of Schizophrenia on Hypertensive Age-Related Changes of the Heart: Acceleration of Hypertensive Changes

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Abstract

Patients with schizophrenia have twice higher mortality rate compared with the general population, a 20 year reduction in life expectancy, and increased risk of cardio metabolic diseases. The anatomical and physiological changes in heart structures are yet to be elucidated in hypertensive patients with schizophrenia. We have investigated echocardiographic parameters in two groups of hypertensive patients of different ages and compared them with the parameters of schizophrenic patients with hypertension. We retrospectively examined 250 patients with diagnoses of hypertension, and after excluding comorbid diabetes or metabolic syndrome allocated them to three groups: middle age (50-65 years; MN; $n = 11$), middle age with schizophrenia (MS; $n = 9$), and elderly (≥ 70; EN; $n = 15$). Non-parametric Jonckheere-Terpstra trend analysis was used for identifying linear trends across the three groups. Significant interaction effects ($p < 0.05$) were identified for ECHO variables LAD, LVDD, PWD, EF, and LVOT indicating a linear trend between the groups, such that there was an age and schizophrenia dependent linear decrease in PWD, EF, and LVOT (MN > MS >EN), but a linear increase of LVDD and LAD (MN< MS <EN). The findings of the present study demonstrates that middle age schizophrenic patients with hypertension have morphological and hemodynamic changes in cardiac parameters with trends resembling the values of hypertensive elderly patients without schizophrenia, suggesting that schizophrenia may accelerate age-related heart changes in the hypertensive heart (dilated cardiac morphology). Future studies are warranted to investigate the early pathological changes of the hypertensive heart in schizophrenia for developing preventive interventions.

ABBREVIATIONS

LV: Left Ventricle; PWD: Posterior Wall Thickness; LAD: Left Atrial Diameter; EF: Ejection Fraction; ECHO: Echocardiographic; MN: Middle Age; MS: Middle Age Schizophrenics; EN: Elderly; LVDD: Left Ventricular Diastolic Diameter; LVOT: Left Ventricular Outflow Tract; BMI: Basic Metabolic Index

INTRODUCTION

Patients with schizophrenia have twice mortality rate compared with the general population, a 20 year reduction in life expectancy [1], and increased risk of cardio metabolic diseases[2,3]. Although the identification of potential triggering factors linking schizophrenia with high morbidity and mortality include modifiable risk factors, autonomic dysfunctions, and side effects of antipsychotic drugs, it remains elusive how cardiac function and morphology changes with schizophrenia.

Morphological changes in heart anatomy have been previously described in patients with hypertension. In fact, hypertension leads to an increase in left ventricle (LV) end-diastolic septum diameter, posterior wall thickness (PWD), left atrial diameter (LAD), LV mass index and relative wall thickness during diastole [4]. Several pathways explain the progression of heart failure in patients with hypertension, with the classic paradigm being that hypertension leads to concentric LV hypertrophy followed by a transition to failure where the LV dilates and the ejection fraction (EF) decreases [5]. Acute myocardial infarction has also been implicated in the progression of heart failure, and patients with schizophrenia between the ages of 18-34 have a higher risk [6]. However, the anatomical and physiological changes in heart structures are yet to be elucidated in hypertensive patients with schizophrenia.

There are several changes in the anatomical structures of the heart that occur with age. For example, regression models have shown that in healthy adults the PWD increases with age [7]. Increasing age also correlates with an increase in aortic root diameter and LV wall thickness [8]. In addition, anatomical structures of the heart have also being associated

with pathological heart changes, such as PWD and LAD have been described as being independent predictors of paroxysmal atrial fibrillation [9]. But, to the best of our knowledge there are no studies that describe the age-related hypertensive changes in patients with schizophrenia associated with the anatomical structures of the heart using echocardiographic parameters.

Lacking are studies aimed at examining the age-related changes in the anatomical structures of the heart in patients with schizophrenia and hypertension. It is therefore plausible to propose that schizophrenia may adversely impact the age-related changes of the hypertensive heart. The echocardiogram provides anatomic information about the heart making it a suitable equipment to study the effect of age on the heart. Hence, we examined echocardiographic (ECHO) parameters in two groups of hypertensive patients of different ages and compared them with the parameters of schizophrenic patients with hypertension.

MATERIALS AND METHODS

Study Subjects and Design

The present research is a retrospective cross-sectional study. Subjects were selected from a population of 250 hypertensive patients who were admitted to our facility within the last 2 years. The inclusion criteria were as follows: (1) patients with a history of hypertension lasting >5 years, (2) groups were matched for weight, height and (3) no comorbid diabetes or metabolic syndrome. In order to minimize confounders, schizophrenic patients on typical antipsychotics (e.g. chlorpromazine, Haloperidol, Loxapine) were excluded from the study. In attempt to minimize the medication effect of antipsychotics on the heart, yet further understand the chronic changes associated with hypertension and schizophrenia, we included a middle age hypertensive's with schizophrenia. Patients that met inclusion were allocated to one of three groups: middle age (50-65 years; MN; n = 11), middle age with schizophrenia (MS; n = 9), and elderly (≥ 70; EN; n = 15). Schizophrenic patients met criteria according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) [10] and non-schizophrenic patients had not clinical evidence of schizophrenia and other psychiatric histories (Figure 1).

Echocardiography

Patients were examined while supine and head elevated with tissue Doppler technology using LOGIQ-P6 ultrasound system (General Electric, USA). M-Mode dimensions during diastole of LAD, PWD, and left ventricular diastolic diameter (LVDD) were measured. EF and left ventricular outflow tract (LVOT) were also measured. All measurements were taken following the recommendations of the European Association of Echocardiography and the American Society of Echocardiography [11]. We calculated LV mass using the formula LV mass = 0.8 X {1.04[(LVIDd + PWTd + SWTd)3 – (LVIDd)3]} + 0.6 g and RWT = (2 X PWTd)/LVIDd [12].

Statistical Analysis

For testing normality in each of the cardiac parameters we used A Shapiro-Wilk test which was significant ($p<0.05$), and hence data were not normally distributed. For that reason, the non-parametric Jonckheere-Terpstra trend analysis was used for identifying linear trends across the three groups and minimize Type I error [12]. This approach increases power assuming apiori an ordering of the groups in ascending (MN < MS <EN) or descending (MN>MS>EN) sequence in the tested variable. Statistical analyses were performed using IMB© SPSS© version 22.0 (Armonk, New York) (Figure 2).

RESULTS AND DISCUSSION

Results

Data are presented as mean ± SD. Patients characteristics and hemodynamics at rest are presented in Table (1). The mean values for the ECHO parameters in all groups were left atrial diameter (LAD; 3.84 ± 0.82 cm), posterior wall thickness (PWD; 1.10 ± 0.82 cm), ejection fraction (EF; 54.3 ± 10.6%), left ventricular outflow tract (LVOT; 1.02 ± 0.36 cm), and left ventricular diastolic diameter (LVDD; 4.81 ± 0.70 cm). Significant interaction effects ($p < 0.05$) were identified for ECHO variables LAD, LVDD, PWD, EF, and LVOT indicating a linear trend between the groups, such that there was an age and schizophrenia dependent linear decrease in PWD, EF, and LVOT (MN > MS >EN), but a linear increase of LVDD and LAD (MN< MS <EN). The mean values for the ECHO parameters in the MN group were (M ± STDE) LAD 3.45 ± 0.14 cm, PWD 1.17 ± 0.10 cm, EF 57.5 ± 1.79 cm, LVOT 1.20 ± 0.14 cm, LVDD 4.83 ± 0.17 cm. In the MS group the mean values were LAD 3.64 ± 0.21 cm, PWD 1.12 ± 0.08 cm, EF 55.56 ± 2.56 cm, LVOT 0.93 ± 0.06 cm, and LVDD 4.92 ± 0.18 cm. In the

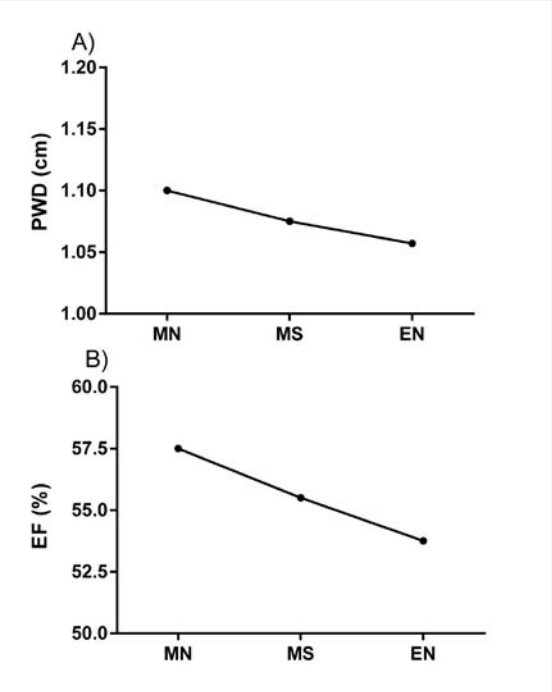

Figure 1 Jonckheere-Terpstralinear trends in selected echocardiographic markers suggesting accelerated aging hypertensive changes in patients with comorbid Hypertension and Schizophrenia
Abbreviations: MN: Middle Age Hypertensive's; MS: Middle Age Hypertensive's with Schizophrenia; EN: Elderly Hypertensive's; PWD: Posterior Wall Thickness; EF: Ejection Fraction

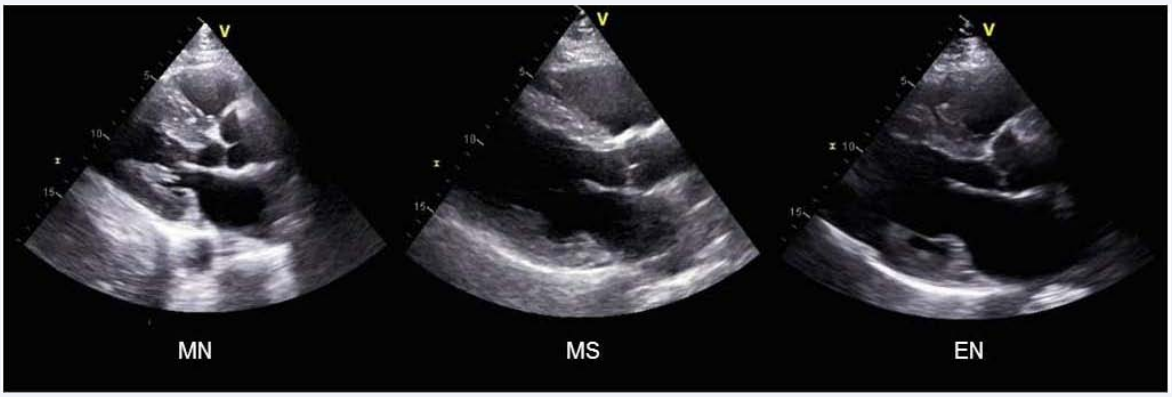

Figure 2 Parasternal Long Axis view (PLAX view) for MN (Middle age hypertensive's), MS (Middle age hypertensive with Schizophrenia), EN (Elderly hypertensive's). MN: PLAX view shows left ventricular (LV) concentric hypertrophy, posterior wall thickness (PWD) 2.3 cm,Left ventricular diastolic diameter (LVDD)4.5 cm, ejection fraction (EF) was estimated to be 62% by Simpson's method.MS: PLAX view showing mild to moderate dilatation of LV, the LVDD 5.3 cm, PWD 1 cm, EF was estimated to be 50% by Simpson's method. EN: PLAX view showing mild to moderate dilation of LV, the LVDD 5.7 cm, PWD 0.9 cm, EF was estimated to be 45% by Simpson's method.

Table 1: Summarizes demographics and hemodynamics of the groups..

Parameter	MN	MS	EN
Age (years)	57.3 ± 4.5	56.6 ± 5.2	75.8 ± 2.8
Body mass index (kg/m^2)	27.3 ± 2.3	28.3 ± 3.1	26.1 ± 3.3
Years with hypertension	7.1 ± 4.1	6.8 ± 5.7	15.3 ± 6.7
Hear rate (bpm)	76.1 ± 7.9	80.2 ± 8.8	77.1 ± 7.1
Stroke volume (ml/beat)	67.3 ± 6.9	65.3 ± 5.9	64.3 ± 6.9
Cardiac output (L/min)	5.2 ± 1.2	5.0 ± 2.2	5.1 ± 1.5

Abbreviations: MN: Middle Age Hypertensive's; MS: Middle Age Hypertensive's with Schizophrenia; EN: Elderly Hypertensive's

EN group the mean values were LAD 4.22 ± 0.23 cm, PWD 1.09 ± 0.06 cm, EF 53.75 ± 2.46 cm, LVOT 0.99 ± 0.09 cm, and LVDD 4.92 ± 0.21 cm. The percentage of patients with concentric remodeling or concentric hypertrophy for the MN, MS, and EN groups were 72%, 55%, and 60% respectively.

Discussion

The main goal of the present study was to examine the pathological changes associated with Schizophrenia in the hypertensive heart. In our study approach was plausible to use age-related hypertensive changes in anatomical heart structures and compare them with the same parameters in hypertensive patients with schizophrenia. We found that PWD, EF, LVOT, LVDD, and LAD mean measurements in the MS group resembled closer to the same measurements in the EN group than in the MN group. These results suggest that there is an aging associated acceleration of hypertensive changes in the heart in patients with Schizophrenia.

Previous studies have shown changes in PWD with age in healthy adults and changes in PWD due to hypertension within the same age group population, both showing an increase in the anatomical heart parameter [4,7]. In our study we observed a decrease in PWD with age. We attribute this to age-related hypertensive changes, due to the fact that all of the patients in our study had diagnoses of hypertension. In addition, middle age patients with schizophrenia had a PWD mean value that was lower than in middle age patients without schizophrenia and closer to the value of elderly patients. We could not find studies that could explain these PWD findings, thus more studies are needed to investigate the age associated hypertensive changes in PWD.

LAD and left atrial enlargement have been identified as independent predictors of first cardiovascular events (stroke, coronary heart disease, congestive heart failure, fatal cardiovascular disease) in middle-aged and elderly adults [13]. LAD is also related to left ventricular hypertrophy and eccentric geometry, greater basic metabolic index (BMI), systolic blood pressure, and age [14]. The results of the present study show that (i) LAD increases with age, (ii) middle age patients with schizophrenia have higher LAD than those without schizophrenia of the same age, and (iii) schizophrenics show an increasing trend in LAD towards the LAD measurements of elderly adults. Thus, the hypertensive pathology pathway that leads to left ventricular hypertrophy involves changes in LAD, which are age-related accelerated in patients with schizophrenia, warranting early treatment interventions in this patient population.

Age-related changes in ventricular volumes have been described in healthy individuals, showing an increase in adolescence and early adulthood followed by a decrease thereafter [15]. Our results show an increase in LVDD with aging, suggesting that an increase in the left ventricular parameter is part of the hypertensive pathology changes. In addition, the majority of patients with diastolic heart failure have left ventricular diastolic volume measurements classified within the normal range [16]. Although, some patients with left heart failure and a normal EF have shown an increased in left ventricular diastolic volume [17]. Our results show that middle age schizophrenics had LVDD measurements with a mean value that was the same as in elderly patients (4.92 cm), suggesting that there is an acceleration of hypertensive changes in the cardiovascular parameter due to Schizophrenia. It remains to be elucidated whether an increase in LVDD could account for early hypertensive pathologic changes of heart failure.

There are 4 categories of heart geometry: (1) normal geometry (RWT ≤ 0.42, normal LVMI), (2) concentric remodeling (RWT> 0.42, normal LVMI), (3) concentric hypertrophy (RWT> 0.42, increased LVMI), and (4) eccentric hypertrophy (RWT ≤ 0.42, increased LVMI) [18]. In our study the percentage of patients with concentric pathology for the MN, MS, and EN groups were 72%, 55%, and 60% respectively. These results suggest the progression of cardiac remodeling with aging from hypertrophy to dilated cardiomyopathy (12% decrease in concentric pathology from middle age to elderly patients), and the acceleration of changes with aging in patients with hypertension and schizophrenia (5% difference in concentric pathology between MS and EN groups).

In healthy individuals EF and stroke volume decrease with age [15]. We observed a decreased in EF with aging, from MN group mean of 57.50% to EN group mean of 53.75%. Furthermore, middle age schizophrenic patients showed a decreased in EF compared with the middle age non-schizophrenics (1.94%). This suggests that schizophrenia changes the anatomical and functional parameters of the heart accelerating the decrease in EF that is normally seen with increasing age. In our study EF values for all subjects were within normal limits, thus diagnoses of heart failure were not applicable.

Aside from the potential antipsychotic-induced deleterious cardiovascular effects, Schizophrenia may extend to individually exude adverse changes in cardiac micro architecture and electrical system [19-21], thus accelerating hypertensive and or age related changes, and hence may increase propensity to arrhythmias [22-24]. For instance, Schizophrenia patients exhibit severe autonomic dysfunction such as low Heart Rate Variability and predominance of sympathetic tone [25,26] independent of their medication status [27,28] suggesting that autonomic dysfunction is a core feature of psychosis pathogenesis. Consequently, beta adrenergic receptor overstimulation causes alterations at the cellular level, namely phosphorylation process, leading to weakened cardiac contractile performance and remodeling [29]. Moreover, drug free Schizophrenics have also been shown to have prolonged QT interval [30], calcium channel dynamics dysregulation [31], and increased thrombogenesis [32] when compared with healthy controls. If taken together, the present study in addition to prior reports seems to add to the notion that cardiovascular risk is not a consequence but rather an inherent component of Schizophrenia.

The present study has some limitations. First, antipsychotic drugs may have adverse effects in the heart of the patients with schizophrenia. However, middle aged medication naive patients with chronic schizophrenia are rare to find, especially when considering that the disease develops during adolescence and early adulthood [10,33]. Second, the sample size of the groups might be small, but this was mainly due to the exclusion of a large number of hypertensive schizophrenic and non-schizophrenic patients who had comorbid diabetes mellitus and other chronic conditions, which would complicate the interpretation of the results. Finally, we did not include a healthy control group although many of the hypertensive associated changes with aging have been previously described elsewhere [15,34-37], and was not the primary objective of the present study.

CONCLUSION

The findings of the present study demonstrate that middle age schizophrenic patients with hypertension have morphological and hemodynamic changes in cardiac parameters with trends resembling the values of hypertensive elderly patients without schizophrenia, suggesting that schizophrenia may accelerate age-related heart changes in the hypertensive heart (dilated cardiac morphology). To the best of our knowledge, this is the first study that examines the detrimental anatomical and functional heart changes associated with schizophrenia in patients with hypertension. Future studies are warranted to investigate the early pathological changes of the hypertensive heart in schizophrenia for developing preventive interventions.

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