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## Original Article

# Influence of an age factor on the pathomorphology of a heart at the antipsychotic cardiomyopathy

Vladimir P. Volkov<sup>1</sup>

<sup>1</sup>Tver center of judicial examinations, Tver, Russia

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## Abstract

**Background.** Currently, the life expectancy of mental patients has increased significantly, which is accompanied by an increase in the duration of antipsychotic therapy and the time of cardiotoxic side effects of antipsychotics, which is fraught with the development of neuroleptic cardiomyopathy (NCMP). In parallel, natural ontogenetic involutonal processes develop in the heart. How joint influence of these two factors is reflected in a morphologic condition of a heart – this question remains open.

**Methods.** The autopsy protocols of 140 patients with schizophrenia (83 men and 57 women) who died at the age under 35 years and over 55 years were analyzed. The morphometric method of a research and calculation of the Coen's coefficient (d'C) determined force of influence of an age factor on pathomorphological changes of heart at various levels of its organization at development of an antipsychotic cardiomyopathy.

**Results.** There is pronounced and statistically significant ontogenetic changes in four of the six organometric parameters. The influence of the aging on two parameters corresponds to an average degree, on one – insignificant, and on others – small. In the presence of NCMP one indicator expressed very weakly only. The sizes d'C for all compared indicators are small and insignificant. With aging the all structural myocardial components are damaged in persons without NCMP. On the contrary, in the presence of NCMP one indicator expressed very weakly only. The sizes d'C for all indicators are small.

**Conclusion.** In patients of different age, the crucial importance in the genesis of pathological changes of the heart at the different levels of its organization has not an age factor, but the side cardiotoxic effect of antipsychotics.

**Keywords:** Antipsychotics, cardiotoxicity, neuroleptic cardiomyopathy, pathomorphology of heart, levels of organization, morphometry, influence of age.

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Corresponding Author: Vladimir P. Volkov, MD. Tver center of judicial examinations, 170008, A. Zavidov St., 24, of. 6, Tver, Russia, E-mail: [patowolf@yandex.ru](mailto:patowolf@yandex.ru) DOI: 10.5455/ww.302644222

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## Introduction

As a result of active therapy of both the main mental and concomitant somatic pathology, the life expectancy of mental patients, in particular those suffering from schizophrenia, has increased significantly.<sup>1,2</sup> This process is accompanied by a significant increase in the duration of antipsychotic therapy (APT), thereby significantly lengthening the time of damaging cardiotoxic effects of antipsychotics (AP) on the heart, which is fraught with the development of severe life-threatening iatrogenic pathology – neuroleptic cardiomyopathy (NCMP).<sup>[3-6]</sup> In parallel, natural ontogenetic involutinal processes develop in the heart.<sup>7</sup>

How these two factors interact among themselves and how their joint influence is reflected in a morphologic condition of a heart – this question remains open. In the special literature any information on this problem is not found. Meanwhile, the clarity is of a great practical importance, since AP is usually prescribed by the psychiatrists, who are usually poorly informed about the nuances of cardiology.<sup>8</sup>

According to the modern doctrine of morphology as the science, is not enough only one descriptive method of a research for the correct and objective characteristic of observed pathological changes; it is insistently necessary to use objective criteria of functional morphology and to be guided by the principle of unity of pathology at various research levels; this principle was postulated by G.G. Avtandilov in the past.<sup>9,10</sup>

Therefore, the research of a morphologic functional condition of heart at patients with NCMP with use of the morphometric methods of a research meeting the modern requirements of evidential medicine<sup>11,12</sup> and allowing to the received results and the draw conclusions as final values of the studied parameters have the quantitative form is represented relevant and can be rather easily analyzed statistically.<sup>9,10</sup>

The purpose of this study is to eliminate – at least, partially – the existing gap by studying the effect of age on macroscopic changes in the heart (organ level of its organization) in patients with NCMP.

## Materials and Method

The autopsy protocols of 140 patients with schizophrenia (83 men and 57 women) who died at the age under 35 years and over 55 years were analyzed. The final diagnosis of each deceased was verified at the autopsy.

The criteria of an exception were the expressed signs of a metabolic syndrome (the increased body weight, arterial hypertension, a diabetes mellitus), a chronic pulmonary pathology with hypertension in a small circle of blood circulation, a cachexia.

The observations were divided into four groups: I and II were respectively 42 young and 39 elderly patients receiving AP but had no heart disease and died of non-cardiac causes; groups III and IV included 27 young and 32 elderly patients suffering from NCMP.

At the macroscopic (organ) level the following parameters were measured: mass of heart (m), linear sizes, perimeter of openings of venous valves, thickness of a wall of ventricles. For the analysis of the obtained data we used the original author's method developed by us for such researches<sup>13</sup>.

For this analysis the external volume of heart without auricles (V) was determined and two relative parameters are calculated (both as a percentage):

1) Cv - volume coefficient, this coefficient shows a part of total amount of heart (without auricles), and this part is the share of the volume of cavities of ventricles,

2) Cl - the coefficient of a left ventricle, this coefficient shows the volume size of a left ventricle of rather total amount of both ventricles. Besides, two other parameters which use gravimetric characteristic of heart (m) were calculated: mass and volume relation (MVR) and index of density of a myocardium (IDM).

Growth of MVR testifies to a myocardium hypertrophy, and its reduction an expansion of cavities of ventricles of heart. IDM clearly demonstrates pronounced correlation with such objective parameters of a microstructure of a cardiac muscle as a stromal and parenchymatous ratio (SPR) and speed of interstitial hypostasis (RIE)<sup>13</sup> which quantitatively describe a condition of its intercellular matrix.

The myocardium of 18 young (men – 10, women – 8) and 43 elderly patients (men – 32, women – 11) distributed in four selected groups as follows: I – 12, II – 6, III – 20, IV – 23 – was studied micro morphometrically.

Myocardium cuts from various departments of the left ventricle filled with paraffin, cuts painted hematoxylin and eosin. The corresponding objects were studied in 10 various fields of a microscope, with necessary increases with the help of an ocular micrometer, the method of calculation of points was also used.<sup>9,10,14</sup> Such parameters as the zone of pericapillary diffusion (ZPD), the index of Kernogan (KI), SPR, RIE are calculated. Carried out a cardiometry and a cytometry of cardiomyocytes (CMCs), determined specific volumes of hypertrophied CMCs (SVHT), atrophied (SVAC) and – method of polarizing microscopy – the specific volume of dystrophic (SVDS). The above-named parameters describe a condition of three structural components of a myocardium: microcirculatory course (ZPD and KI), intercellular matrix (SPR and RIE) and parenchyma (SVHC, SVAC and SVDC).

Mathematical analysis of the obtained quantitative data included the calculation of such an index as the effect's size by J. Cohen,<sup>15,16</sup> which in quantitative terms determines the effect of the studied factor on a particular object of study.<sup>15,17</sup>

It is believed that the inclusion of the Cohen coefficient (d'C) in the mathematical data processing tool strengthens the rigor of the study and gives more weight to the analysis, conclusions and recommendations.<sup>18</sup>

The following gradation of d'C is accepted: insignificant – less than 0,20; small – 0,20–0,49; average – 0,50–0,79; big – 0,80 and above.<sup>15,17,19</sup> Negative d'C values indicate the opposite direction of the effect.<sup>19</sup>

The obtained quantitative results were processed statistically (computer program "Statistica 6.0") with the level of significance of differences of 95% and more ( $p \leq 0.05$ ). The d'C calculation is performed automatically using a computer calculator.<sup>19</sup>

## Results

The comparison of the studied indices in groups I and II (Table 1) identifies the pronounced and statistically significant ontogenetic changes in four of the six parameters.

The calculation of d'C in the compared groups I and II (Table 2) shows that the influence of an age factor on such organometric parameters of the heart as m and IDM corresponds to an average degree, on Kv – an insignificant one, and on the others – a small one. The data presented in both tables are fully consistent.

Very weakly expressed the age-related morphological changes of the heart on the pathological background created by the presence of NCMP are statistically significant only in such an indicator as KI (table 1 – group III and IV).

The sizes d'C for all compared indicators in groups III and IV (Table 2) are in limits of borders small and insignificant. Quantitative results of the conducted morphometric studying of a myocardium on groups of a research and results of the calculation of d'C are presented in tables 3 and 4.

**Table 1. Macroscopic parameters of the heart in the study groups**

Indicators Groups	m	V	K <sub>v</sub>	K <sub>i</sub>	MVR	IDM
	<b>I</b>	<b>283</b> ±7 2-4	<b>127.1</b> ±5.8 3.4	<b>32.0</b> ±0.5 3.4	<b>40.0</b> ±0.5 2.4	<b>2.22</b> ±0.07 2
<b>II</b>	<b>312</b> ±6 1.3.4	<b>134.7</b> ±6.7 3.4	<b>32.2</b> ±0.5 3.4	<b>38.5</b> ±0.6 1.3.4	<b>2.32</b> ±0.06 1.3.4	<b>4.60</b> ±0.12 1.3.4
<b>III</b>	<b>350</b> ±13 1.2	<b>160.2</b> ±6.3 1.2	<b>41.9</b> ±0.7 1.2	<b>39.7</b> ±0.7 2.4	<b>2.18</b> ±0.05 2	<b>6.09</b> ±0.17 1.2
<b>IV</b>	<b>367</b> ±12 1.2	<b>170.1</b> ±8.1 1.2	<b>42.3</b> ±0.9 1.2	<b>40.8</b> ±0.09 1-3	<b>2.15</b> ±0.07 2	<b>6.30</b> ±0.16 1.2

Note: 1-4 – statistically significant differences between the groups

**Table 2. Cohen's coefficient (d'C) in the study groups**

Indicators Groups	m	V	K <sub>v</sub>	K <sub>i</sub>	MVR	IDM
	<b>I-II</b>	0.789	0.204	0.069	-0.452	0.271
<b>I-III</b>	1.285	1.084	3.243	-0.098	-0.129	2.469
<b>II-IV</b>	1.096	0.837	2.589	0.804	-0.456	2.146
<b>III-IV</b>	0.265	0.261	0.095	0.453	-0.094	0.248

**Table 3. Micromorphometric parameters of the myocardium in the study groups**

Indicators Groups	Microvasculature		Intercellular matrix		Cardiomyocytes		
	ZPD	KI	SPR	RIE	SVHC	SVAC	SVDC
<b>I</b>	<b>105.5</b> ±8.4 2-4	<b>1.17</b> ±0.05 2-4	<b>6.5</b> ±1.7 2-4	<b>4.0</b> ±0.9 2-4	<b>5.7</b> ±1.1 2-4	<b>1.9</b> ±0.3 2-4	<b>1.3</b> ±0.5 2-4

<b>II</b>	<b>122.8</b> ±10.4 1.3.4	<b>1.33</b> ±0.07 1.3.4	<b>11.4</b> ±2.1 1.3.4	<b>13.3</b> ±1.6 1.3.4	<b>19.3</b> ±1.7 1.3.4	<b>10.6</b> ±0.9 1.3.4	<b>4.0</b> ±0.7 1.3.4
<b>III</b>	<b>238.3</b> ±14.2 1.2	<b>1.51</b> ±0.12 1.2	<b>56.1</b> ±3.7 1.2	<b>58.8</b> ±2.9 1.2	<b>24.6</b> ±1.9 1.2	<b>32.7</b> ±3.2 1.2	<b>24.3</b> ±1.3 1.2
<b>IV</b>	<b>253.6</b> ±11.8 1.2	<b>1.69</b> ±0.15 1.2	<b>61.1</b> ±4.1 1.2	<b>62.3</b> ±3.3 1.2	<b>26.8</b> ±2.7 1.2	<b>37.3</b> ±3.4 1.2	<b>26.1</b> ±1.9 1.2

**Note: 1-4 – statistically significant differences between the groups**

**Table 4. Cohen's coefficient (d'C) micromorphometric parameters of the myocardium in the study groups**

Indicators Groups	Microvasculature		Intercellular matrix		Cardiomyocytes		
	ZPD	KI	SPR	RIE	SVHC	SVAC	SVDC
<b>I-II</b>	0.653	0.981	0.914	2.923	3.679	6.237	1.657
<b>I-III</b>	2.551	0.794	3.735	5.362	2.719	2.771	4.978
<b>II-IV</b>	2.567	0.563	3.36	3.486	0.649	1.851	2.738
<b>III-IV</b>	0.262	0.287	0.28	0.246	0.203	0.306	0.237

Comparison of all studied indicators in groups I and II (Table 3) reveals the pronounced and statistically significant ontogenetic changes expressed to varying degrees but having the identical focus on ascending. The sizes d'C for all compared indicators are very high (Table 4).

On the contrary, with the development of NCMP (group III and IV) all morphometric parameters of the myocardium remain practically unchanged – the differences between them are statistically insignificant.

The sizes d'C for all indicators are very monotonic and are located near the lower boundary of the gradation interval, designated as "small" (Table 4).

## Discussion

The analysis of the results allows allocating the following key points.

In the absence of NCMP, noticeable and statistically significant changes in almost all organometric parameters of the heart are observed. So, with age m accrues while V though also increases, but only at the level of a trend. Owing to this fact the level of MVR too, although slightly, but still statistically significant, raises. The value of Kv practically does not change, which indicates the absence of the age-related expansion of the cardiac ventricles. On the contrary, the ratio of the ventricular volumes changes with age in favor of the right, as in group II Kl goes down considerably and statistically significantly. All this indicates an age-related hypertrophy of the heart with some degree of the right ventricular dilation.<sup>13</sup>

In old age IDM also increases significantly. This is not surprising, since it is established that this indicator reflects changes in the intracellular matrix of a myocardium, in particular, the degree of myofibrosis,<sup>13</sup> which is often observed during the age-related involutivity processes occurring in a heart muscle.<sup>7</sup>

In the course of a cardiac remodeling in the development of NCMP there is a leveling effect of the latter on the severity of ontogenetic shifts of the organometric parameters. The statistically significant growth only one parameter (KI) reflects some prevalence of an enlargement of the left ventricle compared to the right one.<sup>13</sup>

The calculated low sizes d'C indicate that the force of the influence of an age on the macroscopic condition of the heart in patients suffering from NCMP is extremely small, and all the identified changes are caused by the development of this iatrogenic pathology.

The results of a comparative analysis of the dynamics of indicators in paired groups I-III and II-IV (Table 1), that is in persons of the same age respectively without NCMP and in the presence of one, once again convincingly confirm the proposed situation. In both pairs of the compared groups, the development of NCMP leads to a marked remodeling of the heart, which is documented by the statistically significant changes in the vast majority of the studied organometric parameters. The power of an influence ("size effect") of the development of NCMP at any age for the vast majority of the studied quantitative indicators is very high. (Table 2) This fact proves the crucial importance of NCMP in cardiac remodeling at the organ level of the organization definitively.

Thus, the carried-out analysis of the dynamics of macro morphometric parameters of the heart in the aspect of ontogenesis and the development of NCMP shows the absence of any significant influence of an age factor on the state of the studied organ in the presence of NCMP.

The analysis of quantitative results of the conducted morphometric studying of a myocardium on groups of a research and results of the calculation of d'C allows allocating the following key points.

There are the pronounced and statistically significant ontogenetic changes of all studied indicators of the myocardium in the absence of NCMP. This indicates that as the body ages the all structural components of the heart muscle – microvasculature, stroma (extracellular matrix), and parenchyma (CMCs) – are deeply damaged.

During ontogenesis the processes of microcirculation in the myocardium and collagenogenesis in its extracellular matrix are gradually disturbed, which is accompanied by the development of interstitial edema and myofibrosis, which, in turn, lead to parenchymatous damages. At the same time, along with the phenomena of compensatory-adaptive nature, a dystrophic-degenerative and an atrophic change that significantly reduce the contractile reserves of the myocardium and cause an age-related increase in manifestations of myocardial dysfunction are deployed at an advanced rate.

The calculation of d'C in the compared groups I and II confirms the strong influence of an age factor on the structure of the heart muscle in persons without cardiac pathology.

On the contrary, with the development of NCMP (group III and IV) its leveling effect on the degree of severity of ontogenetic shifts in the myocardium is observed. That is NCMP causes so deep morphological injuries of a myocardium that the age changes on such pathological background are practically not caught.

This is also evidenced by the monotonic values of d'C for each compared indicator (table 4) which are near the lower limit of the gradation interval designated as "small". This suggests that the strength of the influence of age on the state of a cardiac muscle in patients suffering from NCMP is extremely small, and all the identified changes are due to the development of specified iatrogenic pathology.

The results of a comparative analysis of the dynamics of indicators in paired groups I-III and II-IV, that is in persons of the same age respectively without NCMP and with the development of such, confirms this thesis once again convincingly. In both pairs of the compared groups, NCMP is accompanied by deep and statistically significant pathomorphological shifts in the myocardium, affecting all its structural components (Table 3).

It is important to note that "size effect" of the development of NCMP at any age for the vast majority of the studied quantitative indicators is very high (Table 4).

Thus, the carried-out analysis of the dynamics of the morphometric parameters of a myocardium in the aspect of ontogenesis and the development of NCMP shows the absence of any significant influence of an age factor on the condition of the heart muscle in mentally ill patients in the presence of NCMP.

## Conclusion

Generalizing everything told, it is possible to note that at development of NCMP in patients of different age the crucial importance in genesis of various pathological changes of heart at the different levels of its organization (organ, fabric and cellular) has not an age factor, but the side cardiotoxic effect of AP leading finally to development of NCMP.

## Author contributions

VPV took care of the patient and made the literature research, drafted the manuscript and supervised the manuscript. The final version has been read and approved by all authors.

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## Conflict of interest

All authors declare that they have no conflict of interest.

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