# Morphogenesis of a Neuroleptic Cardiomyopathy:A Morphometric Study

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**Abstract:** *Aim:* A comparative morphometric study of heart condition on various organizational levels (organ, tissue, and cellular one) in each clinical stage of neuroleptic cardiomyopathy.

*Methods and results:* Morphometric methods of research were used which meet modern requirements of the evidence-based medicine. For analysis of data from organometry of heart an own original method was used. For this analysis the outer volume of heart without atria (V) was determined and two relative parameters (both in percent) were calculated: 1) Cv - coefficient of volume, this coefficient shows a part of the total volume of heart (without atria), and this part falls on the volume of cavities of ventricles; and 2) Cl - coefficient of the left ventricle, this coefficient shows the volume size of the left ventricle with respect to the total volume of both ventricles. In addition, two other parameters were calculated which use a gravimetric characteristic of the heart (m): mass-volume ratio (MVR) and index of density of myocardium (IDM).

It was found that on the organ level the process of cardiac remodeling ends during the latent stage of the disease. Progression of myocardial dysfunction is connected with changes of myocardium microstructure.

The studied micromorphometric parameters describe the condition of three structural components of myocardium (vasculature, intercellular matrix, and parenchyma). Such parameters as zone of pericapillary diffusion (ZPD), Kernogan index (KI), SPR, RIE were calculated. Karyometry and cytometry of cardiomyocytes (CMCs) were performed, the specific volumes of hypertrophied CMCs (SVHC), of atrophied ones (SVAC), and – by the method of polarization microscopy – the specific volume of dystrophic ones (SVDC) were determined.

In the latent stage the microcirculatory disorders prevail. In the full-scale stage the damages of intercellular matrix come to the forefront. For the terminal stage the atrophic and dystrophic-degenerative changes of cardiomyocytes are characteristic.

*Conclusion:* In the course of morphogenesis of a neuroleptic cardiomyopathy a certain staging of clinical manifestations of the disease is observed; this staging corresponds to an observed cardiac remodeling on the organ level and to an observed chain of interconnected pathologic shifts in all microstructures of myocardium.

**Keywords:** Neuroleptic cardiomyopathy, Morphogenesis, Remodeling of heart, Structural damages of myocardium, Morphometric research.

## INTRODUCTION

Neuroleptic cardiomyopathy (NCMP) is one of serious complications of psychotropic therapy, this complication is caused by a side cardiotoxic effect of antipsychotic drugs [1-4]. To number of the last treat as classical preparations (chlorpromazine, haloperidol, levomepromazine, loxapine, perphenazine, pimozide, thioridazine, trifluoperazine, etc.), and atypical antipsychotics (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone, etc.).

NCMP passes through 3 stages in its development: 1) a latent one, clinically fully compensated one, 2) a full-scale one, when cardiac disorders are clearly detected, but without evident signs of congestive heart failure (CHF), and 3) a terminal one, when the clinical picture of CHF comes to the foreground [9, 11-13].

It is well-known that all changes of function of some or other organs, tissues and cells are initially caused by their structural damages which are a physical substrate of pathophysiological shifts [9]. It follows from this thesis that various cardiac disorders in patients with NCMP, which are characteristic for a certain stage of the disease, are based on morphologic changes of heart on various organizational levels (organ, tissue, and cellular one), and these changes reflect the morphogenesis of this pathology.

At the same time according to the modern doctrine of morphology as a science, a merely descriptive method of research is not enough for a correct and objective characteristic of pathologic changes being observed; it is strongly necessary to use objective criteria of functional morphology [10, 11] and to be guided by the principle of unity of pathology on various research levels; this principle was postulated by G. G. Avtandilov [10] in the past.

Therefore it seems actual important to research a morphofunctional condition of heart in patients with

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NCMP by use of morphometric research methods which meet modern requirements of the evidence-based medicine [12, 13]. The specified methods allow to receive objective results and to draw reliable conclusions, because final values of the parameters, which are studied, have the quantitative form and can sufficiently easily be analyzed statistically [10, 11].

But until now, a deep comparative morphological study of heart condition on each of the before-named levels and in each clinical stage of NCMP has not been performed.

Therefore the aim of the present study is a comparative morphometric study of heart condition on various organizational levels (organ, tissue, and cellular one) in each clinical stage of neuroleptic cardiomyopathy.

## MATERIAL AND METHODS

It is known that a quantitative morphologic characteristic of changes of each organ in the case of its any pathology must start from a definite "reference point" which is defined by the concept of a "norm" [14]. Therefore at the research beginning the results of autopsy protocols of 100 persons (50 men and 50 women) in the age from 18 to 82 years were analyzed who died from non-cardiac causes and who did not have any accompanying cardiac pathology and this fact was verified by autopsy (group I). The cardiac parameters, which were received in this group, are taken as a relative norm (RN).

Then autopsy protocols of 80 dead persons in the age from 16 to 77 years (60 men and 20 women) were studied, in which the NCMP was revealed by section. In 36 of these patients the disease was in the latent stage (group II), in 15 patients it was in the full-scale stage (group III), and in 29 patients it was in the terminal stage (group IV).

The following parameters were measured on the macroscopic level: heart mass (m), linear dimensions, perimeter of venous valve openings, and thickness of a wall of ventricles. For analysis of the received data we used an original method that we had developed for such studies [15].

For this analysis the outer volume of heart without atria (V) was determined and two relative parameters (both in percent) were calculated: 1) Cv - coefficient of volume, this coefficient shows a part of the total volume of heart (without atria), and this part falls on the volume of cavities of ventricles; and 2) CI - coefficient of the left ventricle, this coefficient shows the volume size of the left ventricle with respect to the total volume of both ventricles. In addition, two other parameters were calculated which use a gravimetric characteristic of the heart (m): mass-volume ratio (MVR) and index of density of myocardium (IDM).

A growth of MVR is evidence of a hypertrophy of myocardium, and its diminution is an indication for dilatation of cavities of heart ventricles. IDM clearly shows a strongly expressed correlation with such objective parameters of microstructure of cardiac muscle as stromal-parenchymatous ratio (SPR) and rate of interstitial edema (RIE) [15], which quantitatively describe a condition of its intercellular matrix.

Myocardium was histomorphometrically examined in 80 cases (group 1 - 22, group 2 - 24, group 3 - 13, group 4 - 21).

Myocardium slices from various departments of the left ventricle were filled in paraffin, cuts were painted by hematoxylin and eoziny. Respective objects were studied in 10 different fields of microscope, with necessary magnifications with the help of an ocular micrometer, the point count method was also used [10, 11, 16]. Such parameters as zone of pericapillary diffusion (ZPD), Kernogan index (KI), SPR, RIE were calculated. Karyometry and cytometry of cardiomyocytes (CMCs) were performed, the specific volumes of hypertrophied CMCs (SVHC), of atrophied ones (SVAC), and – by the method of polarization microscopy – the specific volume of dystrophic ones (SVDC) were determined. The above-named parameters describe a condition of three structural components of myocardium: of microvasculature (ZPD and KI), stroma (SPR and RIE), and parenchyma (SVHC, SVAC and SVDC).

The received results were statistically processed by means of the computer program "Statistica 6.0" and by the nonparametric Mann- Whitney's U-criterion with significance level of distinctions 95% and more ($p \leq 0.05$).

## RESULTS

The results of research which has been conducted on the organ level are presented in the Table **1**. As follows from its analysis, all macroscopic cardiac parameters in the case of NCMP statistically significantly differ from RN. At the same time, no

**Table 1: Macroscopic Characteristic of Heart during NCMP Morphogenesis**

| Gr. | m | V | Kv | Kl | MVR | IDM |
|---|---|---|---|---|---|---|
| I | 300<br>±3,0 | 131,6<br>±6,1 | 32,1<br>±0,5 | 39,1<br>±0,6 | 2,28<br>±0,04 | 4,42<br>±0,08 |
| II | 355<br>±9,0<br>1<br>p=0,041 | 163,5±5,4<br>1 p=0,039 | 41,4<br>±1,0<br>1<br>p=0,033 | 40,2<br>±0,7 | 2,17<br>±0,04 | 6,06<br>±0,06<br>1<br>p=0,031 |
| III | 358<br>±12,0<br>1 p=0,034 | 165,8±6,8<br>1 p=0,031 | 42,6<br>±1,7<br>1 p=0,031 | 40,3<br>±0,8 | 2,16<br>±0,06<br>1 p=0,036 | 6,24<br>±0,06<br>1 2 p=0,029 p=0,040 |
| IV | 361<br>±10,0<br>1 p=0,034 | 167,5±5,1<br>1 p=0,029 | 43,2<br>±1,5<br>1 p=0,030 | 40,6<br>±0,7<br>1 p=0,039 | 2,15<br>±0,05<br>1 p=0,036 | 6,36<br>±0,05<br>1 2 3 p=0,026 p=0,037 p=0,043 |

Note: 1 – statistically significant distinctions with gr. I
2 – statistically significant distinctions with gr. II
3 – statistically significant distinctions with gr. III

significant differences of m, V and MVR were found in various clinical stages of NCMP.

The dynamics of values Cv has the same character. At the same time, the values Cl differ from RN only in the terminal stage of NCMP, and to a significantly lesser degree than Cv.

Changes of IDM are the most important ones. The values of this parameter grow already in the latent stage of NCMP (group II) and steadily progress later on.

A comparison of parameters of myocardium microstructure in the groups, which were studied and monitored, among themselves reveals definite regularities (Table **2**). First of all, a considerable and statistically significant difference of all parameters, which were calculated in the case of NCMP, from the same parameters in the case of RN is observed. On the other hand, the parameters, which describe

Conditions of some or other morphologic structures of myocardium in various stages of NCMP, behave differently. For example, parameters, which describe the microvasculature, do not practically change throughout the whole disease. A certain observed growth of their values statistically remains on the level of a tendency.

On the contrary, parameters of intercellular matrix of myocardium in the full-scale and terminal stages of NCMP (groups III and IV) statistically significantly differ not only from RN, but also from these parameters in the latent stage too.

The dynamics of changes of CMCs is distinctive too. For example, such parameter as SVHC is the highest in the group II and it subsequently declines and reaches the level of RN in the group IV. As to the values of SVAC and SVDC, they steadily grow in the course of NCMP development and considerably differ in each subsequent group of monitoring from these values in the preceding ones.

## DISCUSSION

According to analysis of detected changes of heart, which take place on various levels of its organization in different clinical stages of NCMP, we think that the disease has the following morphogenesis.

In the case of NCMP the cardiomegaly develops already during the latent stage of the disease and does not distinctly progress subsequently. This is proved by the absence of significant differences of m, V and MVR in different clinical stages of NCMP.

At the same time, changes of Cv and Cl tell about an uniform dilatation of both heart ventricles with some predominance of the left one, only in the late phases of NCMP morphogenesis (terminal stage). On the contrary, an initially progressive growth of IDM tells about the developing damages of myocardium microstructure, in particular, about changes of its intercellular matrix.

**Table 2: Morphometric Indicators of a Myocardium during NCMP Morphogenesis**

| Gr. | Microvasculature | | Intercellular Matrix | | Cardiomyocytes | | |
|---|---|---|---|---|---|---|---|
| | ZPD | KI | SPR | RIE | SVHC | SVAC | SVDC |
| I | 111,3±17,9 | 1,22±0,10 | 8,1±5,0 | 7,1±4,6 | 10,2±5,0 | 4,8±3,6 | 2,2±2,6 |
| II | 189,3±51,8<br>1<br>p=0,041 | 1,54±0,21<br>1<br>p=0,039 | 39,2±6,2<br>1<br>p=0,025 | 36,4±6,1<br>1<br>p=0,019 | 37,3±6,1<br>1<br>p=0,016 | 23,6±5,4<br>1<br>p=0,019 | 12,8±4,2<br>1<br>p=0,014 |
| III | 282,5±82,2<br>1<br>p=0,034 | 1,61±0,18<br>1<br>p=0,037 | 70,7±5,2<br>1 2<br>p=0,021<br>p=0,041 | 75,8±5,8<br>1 2<br>p=0,012<br>p=0,042 | 20,1±6,6<br>1 2<br>p=0,026<br>p=0,040 | 36,6±6,1<br>1 2<br>p=0,016<br>p=0,034 | 27,7±5,1<br>1 2<br>p=0,012<br>p=0,033 |
| IV | 289,0±79,1<br>1<br>p=0,033 | 1,70±0,17<br>1<br>p=0,035 | 73,7±4,7<br>1 2<br>p=0,017<br>p=0,039 | 78,8±4,6<br>1 2<br>p=0,01<br>p=0,039 | 16,5±6,4<br>2<br>p=0,029 | 46,1±5,4<br>1 2 3<br>p=0,012<br>p=0,033<br>p=0,044 | 37,4±4,6<br>1 2 3<br>p=0,011<br>p=0,036<br>p=0,041 |

Note: 1 – statistically significant distinctions with gr. I
2 – statistically significant distinctions with gr. II
3 – statistically significant distinctions with gr. III

Thus, the received data are evidence of the fact that the process of the cardiac remodeling, which takes place in the course of NCMP development on the organ level, ends when the disease passes to the full-scale stage. Further progression of a myocardial dysfunction leads to the development of CHF and is determined by the growing changes of microstructure of cardiac muscle and its respective components: of microvasculature, stroma (intercellular matrix) and parenchyma (CMCs). In other words, appearance of clinical manifestations of NCMP is accompanied by transition of cardiac remodeling to the deeper (tissue and cellular) organizational levels.

This thesis is confirmed and convincingly proved by results of morphometric research of myocardium microstructure changes in various stages of NCMP morphogenesis, which correspond to the clinical stages of the disease course.

In the latent stage of NCMP (group II), first of all, disorders of microcirculation are detected, and this is reflected by growth of the values of ZPD and KI. Vascular changes cause considerable pathologic shifts in intercellular matrix of myocardium which manifest themselves through an increase of an interstitial edema and through development of myofibrosis (growing values of RIE and SPR correspondingly). The result of the described pathologic processes is damages of CMCs, these damages initially have a compensatory-adaptive character in the form of a cellular hypertrophy [17, 18]. Atrophic and dystrophic-degenerative parenchymatous changes are observed to a lesser degree.

In the full-scale stage (group III) the evidence of pathologic processes in intercellular matrix of cardiac muscle considerably grows - an interstitial edema, that becomes chronic, as well myofibrosis and small-focal (substitutive) cardio sclerosis. Parameters, which describe the condition of microvasculature, do not statistically differ from the ones in the latent stage of NCMP (group II).

Amount of hypertrophied CMCs considerably decreases, although it remains significantly higher than RN. At the same time, dystrophic and atrophic processes, which take place in CMCs, statistically reliably intensify, and these processes are reflected by statistically significant growth of such parameters as SVDC and SVAC.

Thus, in the full-scale stage of NCMP the vascular disorders do not play the deciding part in the process of disease morphogenesis on the tissue and cellular levels any more, and the main significance is gained by stromal changes which are initially caused exactly by a pathology of microcirculation and which lead to a considerable imbalance of CMCs' fractions.

As the result of the above-said, a further growth of pathologic shifts in myocardium parenchyma take place and the disease passes to the terminal stage (group IV).

In this period the fraction of hypertrophied CMCs continues to decrease and statistically returns to the level of RN. Atrophic and dystrophic-degenerative changes of CMCs distinctly increase and come to the forefront (statistically significant growth of SVAC and SVDC as compared with the group III). These processes are considered as an indisputable indicator of a progressive myocardial dysfunction [17, 18].

Values of other parameters of myocardium microstructure fluctuate on the level of a tendency; their differences from a preceding group of research are statistically insignificant.

These data are evidence that in the terminal stage of NCMP the atrophy and dystrophy of parenchyma have the main significance, which are an outcome of pathologic processes having earlier taken place in microvasculature and in extracellular matrix of myocardium. The above-named parenchymatous changes form a physical basis of a final myocardial dysfunction which clinically manifests itself through the development of a fatal CHF.

Thus, a chain of pathologic processes, which develop in heart on the tissue and cellular organizational levels in the course of NCMP morphogenesis, is a distinctive quasi relay-race of structural changes of myocardium. In the initial phase (latent stage), microcirculatory disorders are leaders. Then (in the full-scale stage) the damages of intercellular matrix in the form of the interstitial edema and cardio sclerosis join in and come to the forefront. In the final phase of the disease (terminal stage), the atrophic and dystrophic-degenerative changes of CMCs prevail.

## CONCLUSION

The conducted research has proved that in the course of NCMP morphogenesis not only a certain staging of clinical manifestations of the disease is observed, but also a chain of interconnected and interdependent pathologic shifts in all myocardium structures, which corresponds to this staging - shifts in microvasculature, stroma and parenchyma.

In addition, in the latent stage of the disease the microcirculatory disorders have the deciding significance in the progression of the pathology; subsequently, they gradually lead to stromal changes and through them to damages of CMCs.

In the full-scale stage of NCMP the vascular processes go to the sidelines, and the pathologic shifts in intercellular matrix gain the leading role. In addition, at the same time the damages of parenchyma increase and their compensatory-adaptive character (hypertrophy of CMCs) is replaced by predominance of atrophic and dystrophic-degenerative cellular changes.

In the terminal stage the key pathogenetic factors are atrophy and dystrophy of myocardium parenchyma. They are a physical basis for development of a severe CHF and they proceed against the background of earlier changes of microvasculature and stroma of cardiac muscle.

The above-named micro structural pathologic shifts in cardiac muscle correspond to cardiac remodeling on the organ level. In the latent stage of the disease, the macroscopic cardiac remodeling reflects the compensatory-adaptive processes which are directed towards preservation of the pumping function of heart.

The full-scale stage of NCMP is characterized by termination of remodeling on the organ level, and the further progression of myocardial dysfunction, which is to the maximum expressed in the terminal stage of the disease, takes place because of the above-described pathologic changes of myocardium on the tissue and cellular organizational levels, what leads to a fatal CHF.

## REFERENCES

[1] Volkov VP. Cardiotoxicity of phenothiazine neuroleptics (review of literature). Psichiat psychopharmacother 2010; 12(2): 41-45.

[2] Volkov VP. Phenothiazine dilated cardiomyopathy: some aspects of clinic and morphology. Clin Med 2009; 8: 13-16.

[3] Buckley NA, Sanders P. Cardiovascular adverse effects of antipsychotic drugs. Drug Saf 2000; 23: 215-228. http://dx.doi.org/10.2165/00002018-200023030-00004

[4] Coulter DM, Bate A, Meyboom RHB, et al. Antipsychotic drugs and heart muscle disorder in international pharmacovigilance: data mining study. Br Med J 2001; 322: 1207-1209. http://dx.doi.org/10.1136/bmj.322.7296.1207

[5] Volkov VP. Features of an electrocardiogram at a phenothiazine cardiomyopathy. Upper Volga Med J 2009; 7(4): 3-7.

[6] Volkov VP. Dynamics of arterial pressure at an antipsychotic cardiomyopathy. In: Innovations in science: materials of the XIXth international correspondence scientific and practical conference (on April 22, 2013). Novosibirsk: SibAC Publ 2013: 130-137.

[7] Volkov VP. Morphological features of an antipsychotic cardiomyopathy. In: Medicine: calls of today: international correspondence scientific conference (Chelyabinsk, June, 2012). Chelyabinsk 2012: 33-36.

[8] Volkov VP. Morphometric aspects of a morphogenesis of an antipsychotic cardiomyopathy. Ros J Cardiol 2012; 3: 68-73.

[9] Sarkisov DS, Paltsev MA, Hitrov NK. General pathology of the person. Moscow: Medicine Publ 1995.

[10] Avtandilov GG. Medical morphometry: management. Moscow: Medicine Publ 1990.

[11] Avtandilov GG. Fundamentals of quantitative pathological anatomy. Moscow: Medicine Publ 2002.

[12] Grinkhalkh T. The basics of evidence based medicine / lane with English. Moscow: GEOTAR-MED Publ 2004.

[13] Klyushin DA, Petunin YuI. Evidential medicine. Application of statistical methods. Moscow: Dialectics Publ 2008.

[14] Petlenko VP, Tsaregorodtsev GI. Philosophy of medicine. Kiev: Zdorovja Publ 1979.

[15] Volkov VP. New method of an organometry of heart. In: Paraclinical disciplines: new methods and diagnostic opportunities: the collective monograph / VP Volkov (ed.). Novosibirsk: SiBAK Publ 2014; 78-100.

[16] Gutsol AA, Kondratyev BYu. Practical morphometry of organs and tissues. Tomsk: Tomsk Univer Publ 1988.

[17] Amosova EN. Cardiomyopathies. Kiev: Book plus Publ 1999.

[18] Shumakov VI, Hubutiya MSh, Ilyinsky IM. Dilated cardiomyopathy. Tver: Triad Publ 2003.

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