Hibernation of Myocardium in the Case of Neuroleptic Cardiomyopathy: A Statistical Analysis

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Abstract: *Aim*: The purpose of the present study is to summarize and interpret the data, which has been received earlier, in order to prove the development of the hibernation of myocardium (HM) in cases of the neuroleptic cardiomyopathy (NCMP).

Methods: Morphometric methods of research were used which meets modern requirements of the evidence based medicine. 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), Stromal-parenchymatous ratio (SPR), rate of interstitial edema (RIE) were calculated. Karyometry and cytometry of cardiomyocytes (CMCs) were performed, the specific volumes of hypertrophied CMCs (SVHC), of atrophied CMCs (SVAC) and – by the method of polarization microscopy – the specific volume of dystrophic CMCs (SDVC) were determined.

Results: In the absence of NCMP, the changes, which have an acute character, develop in the case of sudden cardiac death (SCD) and malignant neuroleptic syndrome (NMS) and reflect the statistically significant ($p<0.05$) shifts of the respective quantitative parameters. When NCMP is present, the only parameter, which is significantly changed in connection with SCD and NMS, is SVDC ($p<0.05$).

Conclusion: NCMP causes irreversible damages in myocardium, it leads to its insensitivity, practically almost fully prevents it from reacting to any influences, particularly in the presence of SCD and/or development of NMS. The morphofunctional state of cardiac muscle in the case of NCMP is an independent proof of state of hibernation of myocardium which appears during the process of morphogenesis of NCMP.

Keywords: Neuroleptic cardiomyopathy, Morphometric research, Hibernation of myocardium, Mann-Whitney U-test.

INTRODUCTION

The term "hibernating (dormant) myocardium" is used to describe a distinctive state of cardiac muscle in conditions of its long ischemia [1-4]. When HM is present, the metabolic energy processes in cardio-myocytes (CMC's) are minimized, the contractility of the latter is reduced but their viability is preserved [3, 5].

HM is often observed when different forms of coronary heart disease (CHD) [1, 3, 6, 7] including the ischemic cardiomyopathy (ICMP) [6] are present, and in cases of development of chronic heart failure (CHF) [1]. It seems that HM can be considered as a general pathologic adaptive process which develops in the myocardium when its ischemia of any genesis is present [2-5, 7].

Reports about HM in cases of cardiomyopathies, a diabetic cardiomyopathy [8] and idiopathic dilated one (DCMP) [9] indeed appeared recently. However there are no reports about HM in cases of neuroleptic cardiomyopathy (NCMP) in literature although NCMP belongs to specific (secondary) DCMP's [10] as well as ICMP, but HM is quite often observed in cases of ICMP [6]. It should be said that the clinical course of diseases [11, 12], their pathomorphology [13] and pathogenesis, which is based on myocardial ischemia, have much in common [14, 15].

We conducted our own morphologic study of heart after sudden cardiac death (SCD) had occurred in patients with NCMP or malignant neuroleptic syndrome (NMS) had developed in them and we found that myocardium gets a certain areactivity in cases of NCMP and does not react to such acute stress situations as SCD and NMS [16-18]. It leads to a natural question whether such insensitivity is a sign of presence of HM.

Therefore the aim of the present study is to summarize and interpret the data, which have been received earlier, in order to prove the development of HM in cases of NCMP.

MATERIALS AND METHODS

Myocardium of 169 dead persons was studied who had schizophrenia (men - 105, women - 64; age from

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16 to 77 years) and over the period from a half-year to 30 and more years had received various antipsychotic (neuroleptic) drugs (AD) in amounts which correspond to the therapeutic standard; these medicines were not rarely received in combination with each other.

Criteria of exclusion: CHD, arterial hypertension, heart defects, metabolic syndrome.

The material of study is divided into the following groups (Table **1**): I – 20 patients without any heart pathology who died of acute non-cardiac causes; II – 24 patients who had NCMP and died of various causes, except SCD; III – 13 patients without NCMP in whom SCD was found; IV – 21 patients who had NCMP and suddenly died; V – 58 patients in whom NCMP was observed, without differentiation of the cause of death; VI – 17 lethal cases of NMS without concomitant heart diseases; VII – 16 patients who died of NMS which had developed in the presence of NCMP.

Analysis of data has been conducted in two directions. First, the changes of myocardium microstructure were traced in the cases of SCD and NMS in patients without NCMP in comparison with the group I (comparison of groups I–III and I–VI). Second, the same study was conducted on patients with NCMP (comparison of groups II–IV and V–VII).

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 [19]. Such parameters as zone of pericapillary diffusion (ZPD), Kernogan index (KI), stromal-parenchymatous ratio (SPR) and rate of interstitial edema (RIE) were calculated. Karyometry and cytometry of cardiomyocytes (CMCs) were performed, the specific volumes of hypertrophied CMCs, of atrophied ones and – by the method of polarization microscopy – the specific volume of dystrophic ones were determined. The above-named parameters describe a condition of three structural components of myocardium: of microvasculature (ZPD and KI), intercellular matrix (SPR and RIE), and parenchyma.

STATISTICAL ANALYSIS

The received results were statistically processed by the nonparametric Mann-Whitney U-test with signifycance level of 5%.

RESULTS

In the absence of NCMP, the changes which have an acute character, develop in the case of SCD (comparison of groups' I–III) and reflect the statistically significant ($p<0.05$) shifts of the respective quantitative parameters: decrease of KI, apparent increase of ZPD, RIE and SVDC (Table **2**).

When NCMP is present (comparison of groups II–IV), the only parameter, which is significantly changed in connection with SCD, is SVDC ($p<0.05$).

Table 1: Characteristics of the Studied Material

Groups	The Number of Cases	NCMP +/–	Causes of Death
I APT	20	–	Acute non-cardiac causes of death
II NCMP	24	+	The different causes of death, except SCD
III SCD	13	–	SCD
IV NCMP/SCD	21	+	SCD
V NCMP	58	+	Various acute and chronic diseases, including cardiac pathology (SCD, CHF), suicide, etc
VI NMS	17	–	NMS
VII NCMP/NMS	16	+	NMS

Table 2: Morphometric Indicators of a Myocardium

Groups	Microvasculature		Intercellular Matrix		Cardiomyocytes		
	ZPD	KI	SPR	RIE	SVHC	SVAC	SVDC
I APT	128.5	1.42	10.3	9.8	16.9	8.4	5.7
II NCMP	189.3	1.54	39.2	36.4	37.3	23.6	12.8
III SCD	176.1* p=0.009	1.27* p=0.027	9.1	34.8* p=0.005	15.1	8.6	28.1* p=0.002
IV *NCMP/SCD*	254.3	1.54	38.7	35.9	29.4	19.5	63.7** p=0.002
V NCMP	246.5	1.62	58.8	60.7	25.8	35.2	25.3
VI NMS	177.5* p=0.006	1.48	7.8	33.4* p=0.005	8.9	7.6	17.8* p=0.004
VII *NCMP/NMS*	293.6	1.61	41.6*** p=0.01	69.2	23.2	24.4*** p=0.01	47.6*** p=0.01

Note: APT – antipsychotic therapy

* – statistically significant distinctions with group I

** – statistically significant distinctions with group II

*** – statistically significant distinctions with group V

Development of NMS is accompanied by statistically significant deviations of such parameters as ZPD, RIE, SVDC (comparison of groups I–VI). On the contrary, the comparison of groups V and VII shows that the comorbid pathology (NMS in the presence of NCMP) does not cause such apparent damages of myocardium microstructure. A reliable negative dynamics is observed, like in the cases of SCD, only for SVDC (Table **2**).

DISCUSSION

Myocardium morphology of the patients, who received antipsychotic (neuroleptic) drugs (AD) but hadn't NCMP, are strongly affected both by SCD and NMS [13, 16, 17, 20, 21].

After sudden cardiac death the considerable acute disturbances of microcirculation in the form of paresis of myocardium microvessels are observed, the decrease of value of KI is an evidence of it. It causes the onset of tissue hypoxia with a subsequent increase of permeability of walls of capillary network and with a growth of interstitial edema (apparent increase of RIE). The edema promotes the disconnection of nutritional capillaries and CMC's (growth of ZPD) [22] what seriously impairs the trophism of the latter and is a cause of a quick development of intracellular dystrophic processes (increase of SVDC) [13, 22].

The described changes are the material basis of electrical instability of myocardium and it is fraught with development of severe rhythm disturbances and SCD [20, 21, 23].

Myocardial injuries in course of NMS are a relatively acute process too and are characterized by serious disturbances of microcirculation, interstitial edema and apparent dystrophic degenerative changes of CMC's.

Thus when SCD occurs and/or NMS manifests itself in mentally ill patients without NCMP, pathomorphological changes in myocardium are a standard and rather limited set of disturbances of all its structural components and these disturbances arise acutely. At the same time the reactivity of myocardium is on a quite high level.

NCMP has a leveling influence on the state of myocardium in the case of each of the acute pathologies which are studied. For example, when SCD and/or NMS occur in patients with NCMP, no disturbances of microcirculation are observed. One can believe that deep changes of microvasculature in the case of NCMP, which are the very first to develop already in the latent stage of the disease and which later on become less important [13, 14], deprive myocardium microvessels of the level of reactivity which is inherent in them.

Parameters of state of extracellular matrix (stroma) of myocardium don't have any significant negative changes too. The statistically significant difference of SPR, which is discovered in the case of NMS in the compared groups V-VII, is evidence of a less apparent process of sclerosis of myocardium stroma in the case of comorbid pathology; this difference has no pathogenetic significance for development of myocardial injuries in the case of NMS for the following reasons.

It is known that young and middle-aged persons (from 20 to 40 years) are more often affected in the case of NMS [18, 24]. Therefore the group VII mainly includes patients in whom NCMP appeared relatively recently, *i.e*. it is in the latent or full-scale stage. Myofibrosis is yet relatively moderately apparent in these stages of the disease morphogenesis [13, 14].

On the contrary, the group V includes patients with NCMP whose stage is not taken into consideration, many of them died of CHF in the terminal stage of the disease when the development of myofibrosis is maximally apparent.

The above mentioned circumstances also explain the decrease of SVAC which is found in cases of comorbid course of NMS and NCMP. The only parameter of the studied ones, which responds to development of such fatal situations as SCD and NMS, is SVDC. Its growth in both cases reflect processes of severe damage of CMC's and these processes inevitably progress in the cases of SCD and/or NMS, even in the presence of NCMP.

Thus the quantitative structural parameters of myocardium, whose changes take rather much time (SPR, SVHC and SVAC) - and exactly it is observed in the process of morphogenesis of NCMP [13, 14] - remain without any significant changes when SCD occurs and/or NMS develops. At the same time it is important to emphasize that such acutely developing pathologic processes as disturbances of microcirculation and progression of interstitial edema are not apparent in the cases of SCD and/or NMS in combination with NCMP either.

It follows from what has been said that NCMP causes irreversible damages in myocardium, it leads to its insensitivity, practically almost fully prevents it from reacting to any influences, particularly to the coming of SCD and/or development of NMS. The found morphofunctional state of cardiac muscle in the case of NCMP is analogous to HM which has been described in cases of ICMP [1-3, 6, 7].

CONCLUSION

The conducted morphometric study of changes in myocardium develop in cases of SCD and/or NMS in patients without NCMP on the one hand, and in the presence of the mentioned iatrogenic pathology on the other hand, has discovered significant differences. When NCMP is present, a considerable decrease of reactivity of all studied structural components of cardiac muscle is observed, *i.e*. microvasculature, extracellular matrix and CMC's. This fact is an independent proof of state of HM which appears during the process of morphogenesis of NCMP what has not been so far described in literature.

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