Noncompact Myocardium with Dilated Phenotype: Manifestations, Treatment and Outcomes in Comparison with Other Forms of Dilated Cardiomyopathy Syndrome

Blagova O.V.[1]*, Pavlenko E.V.[1], Varionchik N.V.[1], Sedov V.P.[1], Gagarina N.V.[1], Mershina E.A.[2], Polyak M.E.[3], Zaklyazminskaya E.V.[3], Nedostup A.V.[1]

[1] I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia

[2] Medical Research and Education Center, Lomonosov Moscow State University, Moscow, Russia

[3] B.V. Petrovsky Russian Scientific Center for Surgery, Moscow, Russia

Aim. To study the place of NCM in the structure of DCM, its clinical features and influence on prognosis in comparison with other forms of DCM syndrome.

Methods. The NCM registry includes 125 patients, mean age 46.4±15.1 years, 74 men and 51 women, median follow-up 14 [4.0; 41.0] months. The DCM registry included 365 patients, mean age 46.4±15.1 years, 253 men and 112 women, median follow-up 14 [5; 43.75] months. The examination included electrocardiography (ECG), ECG Holter monitoring, echocardiography, blood anti-heart antibody level evaluation, and additionally cardiac computed tomography, magnetic resonance imaging, DNA diagnostics (in the *MYH7, MYBPC3, TPM1, TNNI3, TNNT2, ACTC1, TAZ, ZASP (LDB3), MYL2, MYL3, DES, LMNA, EMD, TTR* gene panel), coronary angiography, right ventricular endomyocardial biopsy.

Results. The proportion of patients with DCM phenotype in the NCM registry was 40% (n=49), another 11% (n=15) had NCM diagnosed simultaneously with acute/subacute myocarditis. Lethality in these subgroups was 12.2% and 33.3%, respectively, and was significantly higher than in asymptomatic, ischemic and arrhythmic variants of NCM. In the DCM registry, the proportion of patients with NCM was 21% (n=78), and increased left ventricular (LV) trabecularity was detected in another 18% (n=64). DCM patients with and without NCM did not differ by baseline echocardiographic parameters, heart failure class, and cardiotropic therapy. Pathogenic mutations were detected in 14% of DCM patients with NCM and only 3% of other patients with DCM ($p<0.001$). Only in patients without NCM the presence of mutations had a significant effect on lethality. The patients with NCM compared with the others DCM patients showed significantly lower increase in EF in early and late period (from 31.0±10.2 to 34.8±11.0 and 37.1±10.9% [$p<0.05$] vs from 31.8±9.7 to 38.8±11.3 and 42.3±12.4% [$p<0.01$] respectively), a greater incidence of premature ventricular beats (1568 [105;7000] vs 543.5 [77.75; 3194], $p<0.05$), appropriate defibrillator shocks and sudden deaths (17.9 vs 5.9%, $p<0.001$), intracardiac thrombosis (21.8 vs 13.5%, $p=0.069$) despite a greater frequency of anticoagulants (73.1 vs 57.4%, p<0<05). There were no significant differences in death (19.2 vs 18.5%) and transplantation (7.7 vs 3.8%) between patients with and without NCM. There were no cases of NCM regression.

Conclusion. NCM is an independent form of DCM syndrome, which is characterized by higher frequency of pathogenic mutations, arrhythmic events, worse response to cardiotropic therapy, higher frequency of intracardiac thrombosis. The absence of mortality differences can be explained by the higher frequency of preventive interventions in this category of patients with DCM (prescription of anticoagulants, defibrillator implantation, heart transplantation).

Key words: noncompact myocardium, dilated cardiomyopathy, prognosis, lethality, intracardiac thrombosis.

For citation: Blagova O.V., Pavlenko E.V., Varionchik N.V., Sedov V.P., Gagarina N.V., Mershina E.A., Polyak M.E., Zaklyazminskaya E.V., Nedostup A.V. Noncompact Myocardium with Dilated Phenotype: Manifestations, Treatment and Outcomes in Comparison with Other Forms of Dilated Cardiomyopathy Syndrome. *Rational Pharmacotherapy in Cardiology* 2022;18(1):27-35. DOI:10.20996/1819-6446-2022-02-01.

*Corresponding Author: blagovao@mail.ru

Received: 06.05.2021
Accepted: 07.06.2021

Introduction

Non-compact myocardium (NCM) is one of the least studied variants of cardiomyopathies. The European classification of cardiomyopathies classifies it as an unclassified cardiomyopathies [1], there are no recommendations for its diagnosis and treatment, specially planned studies of NCM, and symposiums at congresses in Europe.

The question of the nature of NCM is still unresolved. The genetic causation of the NCM phenomenon is beyond doubt [2], but too many and heterogeneous genes, mutations in which have already been described in patients with NCM, a high frequency of combinations of NCM with other cardiomyopathies (hypertrophic, restrictive) blur the boundaries and cast doubt on the nosological isolation of NCM. There is an opinion about the possible secondary nature of NCM due to significant dilatation of the heart chambers, its overload (sports, pregnancy), certain diseases (sickle cell anemia) [3]. In general, the question is as follows: is NCM a sign, a phenomenon, or a disease [4]?

At the same time, the number of genes potentially responsible for the development of dilated cardiomyopathy (DCM) is even greater, but this doesn't cast doubt on the existence of primary (true) DCM, in contrast to other variants of the DCM syndrome [5]. Probably, the term «syndrome» can also be used in the case of NCM, although in our opinion, the presence of NCM inclines the diagnosis in favor of genetically determined cardiomyopathy. NCM with a dilated phenotype raises the most questions. If other forms of cardiomyopathies tell us about the association with NCM, then the presence of DCM is more often regarded as the most typical NCM phenotype (the so-called non-compact cardiomyopathy).

The aim of this study was not to finally answer the question about the nature of NCM. However, less general questions are important for practical cardiology: 1) are there any differences in patients with NCM and a dilated phenotype from other patients with DCM syndrome; 2) whether these differences require special approaches to the treatment of patients with NCM and DCM phenotype; 3) whether the presence of NCM means a worse prognosis in comparison with other variants of the DCM syndrome.

The aim of our study was to study the place of NCM in the structure of DCM, its clinical features and influence on prognosis in comparison with other forms of DCM syndrome.

Material and methods

125 patients were included in the NCM registry (average age was 46.4±15.1 years; 74 men and 51 women; median follow-up was 14 [4.0; 41.0] months).

Inclusion criteria: age ⩾16 years; the presence of visual criteria for NCM: a two-layered myocardium of the left ventricle (LV) with a non-compact to compact ratio from 2:1 in echocardiography or from 2.3 to 1 in multislice computed tomography/magnetic resonance imaging; synchronous motion of non-compact and compact layers; detection of more than 3 trabeculae in the left ventricle and the presence of intertrabecular blood flow at the end of diastole.

365 patients were included in the DCM registry (average age was 46.4±15.1 years; 253 men and 112 women; median follow-up was 14 [5; 43.75] months).

Inclusion criteria: age ⩾16 years, LV dilatation (end-diastolic size >5.5 cm) and LV systolic dysfunction (ejection fraction [EF] <50%).

Exclusion criteria: myocardial infarction, acute coronary syndrome due to coronary atherosclerosis, infective endocarditis less than 6 months old, acquired heart disease, thyrotoxic and hypertensive heart (LV myocardial hypertrophy >14 mm), verified amyloidosis, storage diseases, sarcoidosis, diffuse connective tissue diseases, systemic vasculitis, heart surgery less than 2 months old, the patient's refusal to participate.

The study was approved by the interuniversity ethical committee. All patients signed a voluntary informed consent for additional examinations.

Examination methods included electrocardiography, Holter monitoring of the electrocardiogram, echocardiography, assessment of the level of anti-cardiac antibodies in the blood by indirect immunofluorescence, as well as multislice computed tomography, magnetic resonance imaging of the heart, DNA diagnostics (in the genes *MYH7, MYBPC3, TPM1, TNNI3, TNNT2, ACTC1, TAZ, ZASP (LDB3), MYL2, MYL3, DES, LMNA, EMD, TTR*), coronary angiography and right ventricular endomyocardial biopsy. The purpose of the extended examination was to identify exclusion criteria, clarify the nosological nature of the DCM syndrome (verify the diagnosis of myocarditis). Clinical variants of NCM were determined in accordance with the previously described criteria [6].

The search for mutations was performed using a targeted panel of genes with two primer pools, the design of which was performed using the automatic online resource Ion AmpliSeq Designer® (Thermo Fisher Scientific, USA). Library preparation was performed using the Ion AmpliSeq™ Library Kit 2.0 following the manufacturer's protocol (Thermo Fisher Scientific). Sequencing was performed on Ion 314™ and Ion 316™ chips using the Ion PGM™ System high-performance semiconductor sequencer. The data obtained from the Ion PGM™ System was processed using the CoverageAnalysis and VariantCaller plugins included in the licensed Torrent Suite Software 5.6.0 and Ion Reporter Software (Thermo Fisher Scientific). Visualization of NGS reads was carried out using the Integrative Genomic Viewer, alignment was carried out on the reference genome according to the hg19 version. The frequencies of the identified genetic variants, as well as in silico bioinformatic analysis, were performed using an internal pipeline, using the ACMG criteria (2015) [7], as well as the Genome Aggregation Database, ClinVar, HGMD, online resources VarSome, PolyPhen2.0, HSF and CardioDB.

Primary endpoints included lethality, sudden cardiac death (SCD), heart transplantation, and «death + transplant» indicator, secondary endpoints included «appropriate defibrillators + SCD» indicator, intracardiac thrombosis, embolic events, and EF changes.

Treatment of patients with DCM syndrome (both with and without NCM) was carried out in accordance with European and Russian recommendations and included optimal drug therapy for chronic heart failure (CHF), implantation of cardioverter-defibrillators and resynchronization devices with a defibrillator function, as well as basic therapy of myocarditis in case of its verification. We will talk separately about the appointment of indirect anticoagulants.

Statistical processing of the material was carried out using the SPSS Statistics 22.0 program (IBM, USA). Quantitative characteristics are presented as mean (M) and standard deviation (δ) or as median (Me) and interquartile range [25%; 75%]. The normality of distribution was assessed using the Kolmogorov-Smirnov's test; the statistical significance of differences was assessed using the Student's, Mann-Whitney's, and Wilcoxon's tests. The construction of Kaplan-Meier's curves was carried out to assess survival. Differences were considered significant at $p<0.05$.

Results

NCM with a dilated phenotype in the structure of the NCM registry

The proportion of patients with NCM and DCM phenotype in the registry of patients with NCM was 40% (n=49), and another 11% (n=15) had DCM syndrome diagnosed simultaneously with acute/subacute myocarditis (Fig. 1). Mortality in these subgroups was 12.2% and 33.3%, respectively, and it was higher than in clinical variants of NCM without

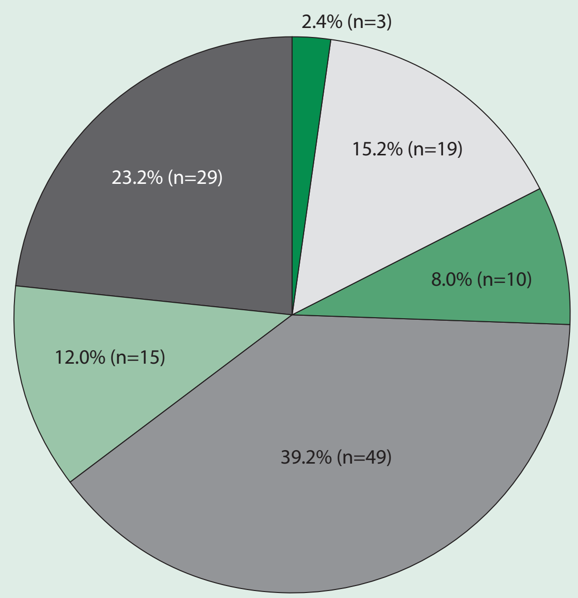


Figure 1. Frequency of different clinical variants in registry of patients with NCM (n=125)

Table 1. Clinical manifestations of non-compacted myocardium with dilated cardiomyopathy phenotype, including combination with acute/subacute myocarditis, in comparison with other non-compacted myocardium variants

Clinical variant	Without symptoms (n=3)	Arrhythmic (n=19)	Ischemic (n=10)	DCM (n=49)	Acute/subacute myocarditis (n=15)	Combination with other cardiomyopathies (n=29)
Age, years	36.0±5.6	43.9±16.6	54.0±15.3	49.7±15.1	43.7±13.2	42.1±14.1
Men, n (%)	1 (33.3)	11 (57.9)	5 (50.0)	32 (65.3)	11 (73.3)	14 (48.3)
Family history, n (%)	0	5 (26.4)	1 (10.0)	9 (18.4)	2 (13.4)	9 (31.0)
LV EF, %	51.6±9.5	53.2±8.8	47.2±10.7	32.9±10.8	27.0±9.0	41.0±14.5
End-diastolic LV size, cm	5.1±0.8	5.4±0.5	5.8±0.6	6.5±0.8	6.5±0.7	5.7±0.7
CHF class (NYHA)	-	0 [0;1]	1 [0;3]	3 [2;3]	3 [2; 4]	2 [1; 3]
Ventricular tachycardia, n (%)	0	8 (42.1)	2 (20.0)	24 (49.0)	10 (66.7)	20 (69.0)
Thromboembolism, n (%)	0	2 (10.5)	3 (30.0)	12 (24.5)	8 (53.3)	5 (17.2)
Myocardial necrosis, n (%)	0	0	4 (40.0)	7 (14.3)	6 (40.0)	3 (10.3)
Implantation of devices, n (%)	0	6 (31.6)	1 (10.0)	20 (40.8)	3 (20.0)	15 (51.7)
Heart transplantation, n (%)	0	0	0	2 (4.1)	1 (6.7)	4 (13.8)
Death, n (%)	0	0	0	6 (12.2)	5 (33.3)	7 (24.1)

DCM – dilated cardiomyopathy, EF – ejection fraction, LV – left ventricle, CHF – chronic heart failure.

Data are presented as M±δ or Me [25%; 75%] unless otherwise stated

significant chamber dilatation - asymptomatic, ischemic, and arrhythmic variants of DCM (Table 1).

Comparison with the «death + transplantation» indicator showed the prognosis of patients with DCM phenotype significantly worse than in patients without significant CHF, especially when combined with acute/subacute myocarditis (Fig. 2). Some patients with “chronic” DCM (without an acute debut less than six months ago) also had myocarditis, but it didn't determine the severity and severity of decompensation. The worst prognosis was observed when combined with other cardiomyopathy (restrictive, hypertrophic, arrhythmogenic right ventricular), but dilatation of the chambers and systolic dysfunction occurred only in some patients in the later stages.

The frequency of NCM in the register of patients with DCM syndrome is shown in Figure 3. The total proportion of patients with NCM in the register of patients with DCM was 21% (n=78). Another 64 patients with DCM had increased LV trabecularity, that is, the ratio of the thickness of the non-compacted and compact layers from 1 to 2. Patients with NCM didn't differ from other patients with DCM syndrome in terms of the main demographic and echocardiographic parameters, the severity of CHF and the volume of cardiotropic therapy (Table 2). Further comparisons focused on more NCM-specific parameters such as genetic background, arrhythmic and thromboembolic events, and outcomes.

The genetic nature of NCM compared with other variants of DCM and its influence on outcomes

The frequency of mutation detection in patients with NCM was significantly higher than in patients with DCM without NCM and amounted to 14% and 3%, respectively ($p<0.001$; see Fig. 3). At the same time, mutations in the genes of sarcomeric proteins predominated in patients with NCM (most often in the *MyBPC3* gene), while the genetic nature in patients without NCM was most often identified in the presence of skeletal myopathy (mutations in the *DES, LMNA, EMD* genes). An assessment of the prognostic significance of the identified mutations showed their significant negative impact on the prognosis (frequency of reaching the “death + transplantation” indicator) in patients with DCM without NCM, while the prognosis didn't change in patients with NCM depending on the detection of the disease genetic nature (Fig. 4).

Influence of non-compacted myocardium on the effectiveness of DCM syndrome complex treatment and the frequency of ventricular ectopy

The influence of non-compact myocardium on the results of complex treatment of CHF (increase in LV

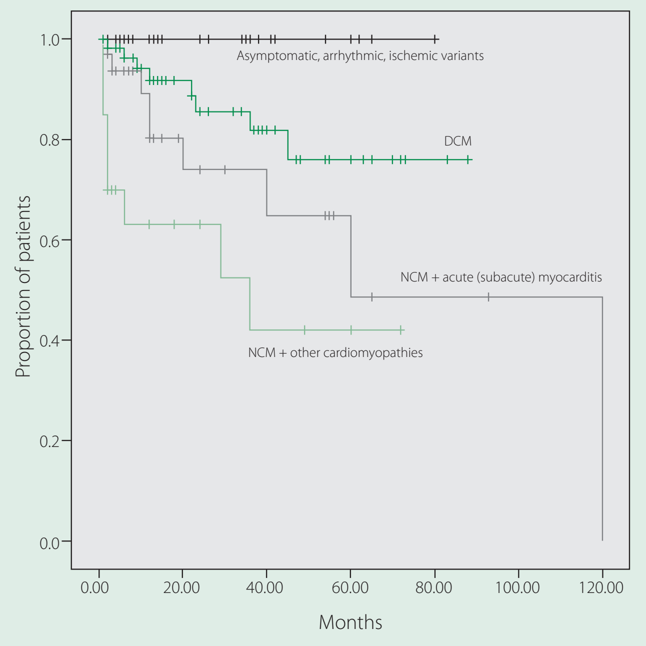


Figure 2. Kaplan-Meier curves for the "death+transplant" rate in the study groups

contractile function) was studied. A significantly worse increase in LV EF was noted in the first 2-4 months of treatment (immediate response to treatment: 38.8±11.3% vs 34.8±11.0%; $p<0.05$) and by the end of the follow-up period (42.3±12.4% vs 37.1±10.9%, respectively; $p<0.01$) between the groups of DCM without NCM and DCM with NCM (31.8±9.7 vs with 31.0±10, 2%; $p>0.05$) with no significant differences. At the same time, there were no significant differences in the frequency of myocarditis (according to both morphological and complex examination data) between patients with and without NCM, which allows us to speak about the independent influence of the NCM presence on the treatment results. NCM regression as a result of improvement in contractility and reduction in LV size was not observed in any case.

Influence of NCM on the frequency of arrhythmic events, thrombosis and embolism in patients with DCM syndrome

Arrhythmias typical of NCM and DCM include atrial fibrillation (AF), ventricular extrasystole, sustained and non-sustained tachycardia, and SCD due to ventricular fibrillation. The median number of ventricular extrasystoles in patients with NCM was significantly higher than in patients without NCM (1568 [105; 7000] vs 544 [77; 3216] ventricular extrasystoles/day, respectively; $p<0.001$). Non-sustained tachycardia was recorded in 54% and 46% of patients, sustained tachycardia was recorded in 10% and 5%, left bundle branch block was recorded in 30% and 26% ($p>0.05$ for all).

The decision to implant defibrillators was more often made in patients with NCM, taking into account the higher frequency of "ventricular extrasystole/tachycardia" and a smaller increase in LV EF. Devices (cardioverter-defibrillator and resynchronization device with defibrillator function) were implanted in 32 patients with NCM (41%) and 60 patients with other variants of DCM (21%), differences are significant ($p<0.01$). Further analysis showed the feasibility of such a solution. The frequency of appro-

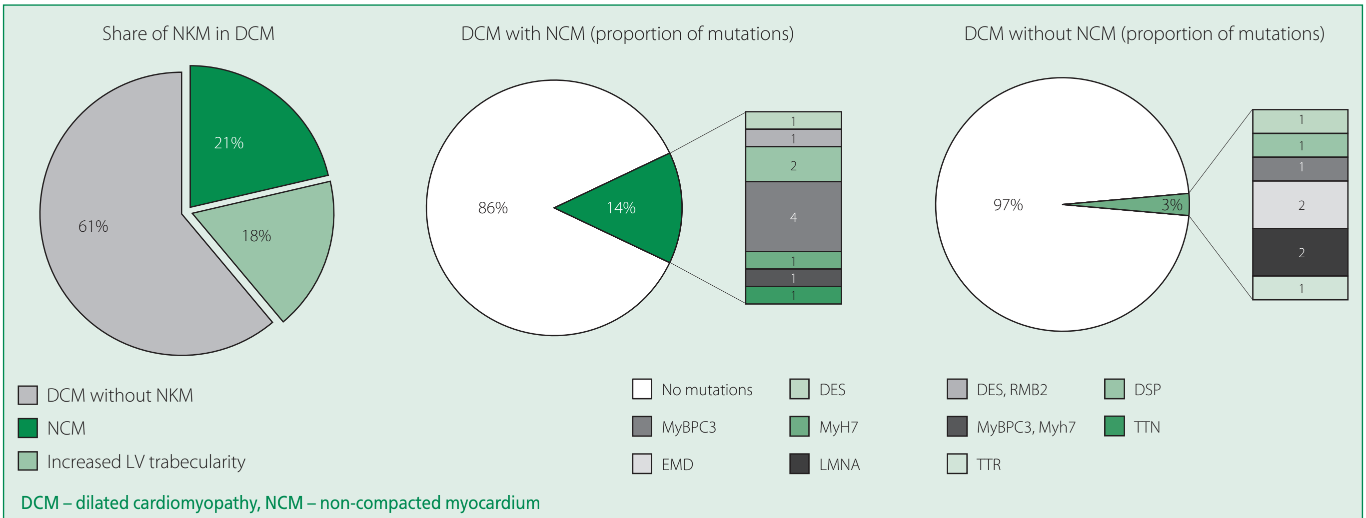


Figure 3. Proportion of noncompact myocardium in the structure of DCM registry and features of its genetic nature in comparison with other variants of DCM

Table 2. Baseline clinical and demographic characteristics of patients with dilated cardiomyopathy syndrome with or without non-compacted myocardium

Parameters	DCM with NCM (n=78)	DCM without NCM (n=287)
Age, years	45.9±14.0	48.5±12.3
CHF class (NYHA)	3 [2; 3]	3 [2; 3]
Prescription, months	30 [6.75; 87.5]	18 [6; 60]
End-diastolic LV size, cm	6.5±0.8	6.5±0.8
End-diastolic LV size, ml	180.6±67.5	195.7±74.6
End-systolic LV size, ml	129.5±60.4	134.3±63.7
LV EF, %	31.0ф10.9	31.8±9.3
LA, cm	4.6±0.8	4.8±0.7
LA, ml	98.7±37.3	105.6±42.0
RA, ml	76.8±38.7	85.3±44.8
RV, cm	3.1±0.7	3.2±0.8
SPPA, mmHg	40.5±16.3	41.2±15.0
ACE inhibitors, n (%)	60 (78.2)	227 (79.0)
Beta-blockers, n (%)	65 (83.3)	241 (84.0)
Amiodarone, n (%)	47 (59.7)	166 (58.1)

DCM – dilated cardiomyopathy, NCM – non-compacted myocardium, CHF – chronic heart failure, LV – left ventricle, EF – ejection fraction, LA – left atrium, RA – right atrium, RV – right ventricle, SPPA – systolic pressure in the pulmonary artery, ACE – angiotensin converting enzyme

Data are presented as M±δ or Me [25%; 75%] unless otherwise stated

p<0.05 for all comparisons between study groups

priate defibrillator responses was significantly higher in patients with NCM compared with patients without NCM (34 and 17%, p=0.061), the frequency of the "appropriate shocks + SCD" indicator was significantly higher in patients with NCM (19% and 6%; p<0.001).

AF was more common in patients with DCM without NCM than in patients with NCM (58% and 67%, respectively). However, indirect anticoagulants were prescribed more often to patients with NCM (73% vs 56%, p<0.05) because also low LV EF was taken into account in this case, regardless of the presence of AF.

In addition, intracardiac thrombosis (28% vs 13%, p=0.069) was more often detected in patients with NCM, which also became the basis for prescribing anticoagulants. As a result, there were no significant differences in the frequency of embolic events in patients with and without NCM (17 and 14%, respectively). In both groups, the most common embolic complication was acute cerebrovascular accident.

Influence of non-compacted myocardium on disease outcomes (primary endpoints)

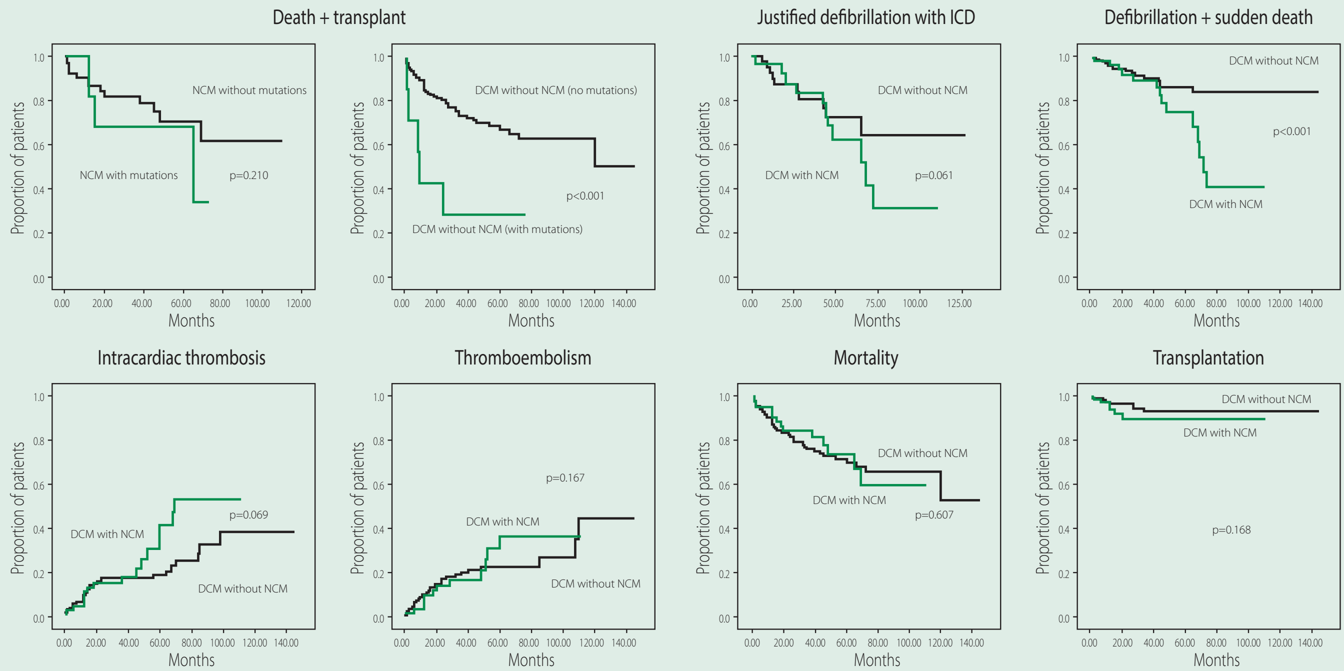
The frequency of reaching the endpoints in patients with DCM and NCM (follow-up period was 22 [12; 47.25] months) and patients with DCM without signs of NCM (follow-up period was 14 [5; 42.25] months) was carried out. No significant differences were found (see Fig. 4): the death rate was 20.5% and 18.5%, heart transplantation was performed in 6 and 11 patients (7.7% and 3.8%), the frequency of reaching the "death + transplantation" endpoint was 24.4% and 20.9%. The most common cause of death in both groups was terminal CHF.

Discussion

The DCM phenotype is well known as one of the most typical manifestations of NCM. There is a point of view that only this phenotype is a manifestation of the true "non-compact cardiomyopathy". The largest registries of NCM in children and adults include this phenotype along with others – asymptomatic, hypertrophic, restrictive, and indeterminate [8, 9]. Towbin J.A. et al also distinguish a mixed (hypertrophic and dilated) phenotype [10].

Our data confirm the heterogeneity of the phenotypic manifestations of non-compact cardiomyopathy and allow for a comparative analysis of dilated phenotype and other phenotypes. The results of this analysis showed a worse prognosis in patients with NCM and DCM phenotype in comparison with asymptomatic, arrhythmic and ischemic variants (combination with subacute myocarditis, as well as with other forms of cardiomyopathy, had an even more serious prognosis). These data are fully consistent with other studies in which the dilated phenotype of DCM prevailed quantitatively (up to 56% of all cases of NCM [11]) and had an even more severe course than the hypertrophic phenotype [8], which is quite expected.

But the main aim of this study was to clarify the place of NCM among all patients with DCM syndrome. A similar analysis in children showed no differences in the frequency of deaths and transplants in patients with NCM and other forms of DCM [8], but comparisons in the frequency of life-threatening manifestations and types of treatment were not made. A more detailed analysis of the outcomes in



DCM – dilated cardiomyopathy, NCM – non-compacted myocardium

Figure 4. Frequency of complications and unfavorable outcomes in patients with noncompaction myocardium compared to other patients with DCM

patients with NCM with a dilated phenotype showed that improvement occurred only in 17% of patients (a decrease in the class of CHF), the condition remained stable in another 33% of patients, while the disease proceeded unfavorably in the second half of the patients – the class of CHF increased in 33%, 17% of patients died [12].

The data that we obtained regarding the prognostic significance of genetically verified forms are interesting. Patients with NCM, in whom pathogenic mutations have been identified to date, had a slightly worse survival rate, but didn't significantly differ from patients in whom mutations have not yet been detected (DNA diagnostics have not been completed). This can be considered as indirect evidence that NCM in the rest of the patients has a genetically determined nature and proceeds in a similar way. The frequency of detection of mutations in patients with NCM varies in the range of 20-30%, and the prevalence of sarcomeric mutations was confirmed in a large recent meta-analysis that included 561 patients with NCM from 172 studies [11]. Also, the association of mutations in the *MyBPC3* gene (predominant in our patients) was shown with presentation in average age, systolic dysfunction, and adverse events in 31% of cases [13]. But the influence of the mutation presence on the development of CHF and arrhythmias was not previously noted [14].

On the other hand, the detection of a pathogenic mutation in our cohort of patients with DCM without NCM turned out to be a negative prognosis factor: mutations were detected significantly less frequently than in NCM and led to a statistically significant increase in mortality. The explanation for this fact is that the proportion of true (primary and genetically determined) DCM in the overall structure of the DCM syndrome is really small – such patients are also likely to be among patients without identified mutations, but they don't determine the prognosis.

The frequency of myocarditis was quite high both in patients with NCM and without it, but if myocarditis only markedly aggravated the course of primary cardiomyopathy in the presence of NCM (and its successful treatment still didn't provide good outcomes), then myocarditis in patients with other forms of DCM often was the leading cause of decompensation, and its treatment gave more noticeable results. The significant differences revealed by us in the severity of a positive response to complex therapy, which was judged by the degree of increase in EF (in the absence of initial differences), can be explained precisely by this in the first place. Patients with NCM had significantly worse immediate response to treatment and its long-term results. The presence of NCM hindered the development of positive effects, including the standard therapy for CHF, which was widely used in all patients with DCM.

Two more clinical manifestations were established, according to which patients with NCM turned out to be more severe than other patients with DCM - ventricular arrhythmias and intracardiac thrombosis. Not only ventricular extrasystole, but also the « appropriate defibrillator triggers + SCD» endpoint turned out to be significantly more frequent in the presence of NCM. Differences in the frequency of thrombosis were insignificant, which confirms the presence of specific mechanisms of thrombosis in the presence of a non-compacted layer. We note that both phenomena would be difficult to explain in terms of secondary NCM, which is common in severe decompensation. In the largest meta-analysis to date, which included 2271 patients with NCM, sustained or non-sustained tachycardia was detected in 17%, thromboembolic events were detected in 9%, appropriate defibrillator shocks were detected in 15%, i.e. less often than in our study [15] .

The established absence of significant differences in the frequency of embolic events between our patients with and without NCM is explained by the more frequent prescription of indirect anticoagulants for NCM. The indications for such treatment were not only AF and detected thrombosis, but also a decrease in LV EF less than 40%, as is currently recommended [16, 17]. This approach has fully justified itself. In addition, AF was somewhat more common in patients with DCM without NCM, which could affect the frequency of embolic events in this subgroup and level the differences.

Finally, we analyzed the frequency of reaching the primary endpoints in DCM patients with NCM and without it. The absence of significant differences in overall mortality and transplantation frequency, which we established, can't be considered as evidence that the presence of NCM doesn't affect the prognosis in patients with DCM in any way, as suggested by some authors who compared on the basis of magnetic resonance imaging [18]. In other studies, such differences were obtained [19].

The leveling of differences seems to us to be a natural (and desirable) result of active influence on the mechanisms of thanatogenesis specific for NCM, namely, more frequent implantation of defibrillators (with equal initial echocardiography parameters) and prescription of anticoagulants. The third mechanism (insufficient response to therapy in the presence of NCM) is not yet subject to correction (with the exception of an earlier decision on heart transplantation), but the category of patients was also in other variants of DCM (with and without myocarditis) that responded poorly to treatment, which requires further study.

Now we will answer the applied questions that were posed at the beginning of this study. Differences in patients with NCM and a dilated phenotype from other patients with DCM syndrome (both genetic and non-genetic and mixed nature) certainly exist, and these differences exacerbate the risk of adverse outcomes and require special approaches to the treatment of patients with NCM and the DCM phenotype. Such approaches are being developed, and their active use to a large extent makes it possible to positively influence the prognosis of patients with NCM and smooth out differences with other types of DCM.

In conclusion, we consider the fundamental question about the nature of NCM. The data obtained allow us to assert that the NCM phenomenon in patients with DCM syndrome in most cases is not a secondary consequence of severe decompensation, but an independent nosological variant. This is confirmed by the following facts:

1. The NCM phenomenon was also detected in the absence of decompensation (and was not explained by pregnancy, sports, etc.).
2. Patients with DCM syndrome of other etiologies, including those with severe myocarditis and primary forms, had no lesser degree of decompensation (they didn't differ in any echocardiography parameter), but NCM was not visualized in them.
3. Patients with a dilated phenotype of NCM had specific differences in the clinical picture from other patients with DCM.
4. Regression of systolic dysfunction and reduction in LV size were never accompanied by the disappearance of the NCM phenomenon.

Study limitations. For objective reasons, DNA diagnostics was not completed in all patients included in the study. Its volume was various in different patients depending on the clinical phenotype. The terms of observation of patients also differed, but they were sufficient in both study groups.

Conclusion

The presence of NCM doesn't initially lead to more pronounced myocardial dysfunction compared to other patients with DCM syndrome but is accompanied by a significantly worse increase in EF during treatment (in the early and late periods). Pathogenic mutations (mainly in sarcomeric genes) were detected significantly more often in patients with NCM than in other patients with DCM. The presence of NCM is accompanied by more aggressive ventricular arrhythmias – a significantly more frequent ventricular premature beats, a greater frequency of appropriate defibrillator responses, and a significantly higher frequency of shocks/sudden cardiac death. The frequency of thrombosis in patients with NCM was not significantly higher, the frequency of thromboembolic complications didn't differ from other patients with DCM due to a significantly more frequent prescription of indirect anticoagulants (with a lower frequency of AF). The frequency of death and transplantation in patients with NCM didn't differ significantly from other patients with DCM, probably due to the timely prevention of sudden death, embolic complications and a positive response to complex treatment with the achievement of a satisfactory level of EF. No regression of NCM was noted in any case against the background of improvement in contractility and reduction in the size of the left ventricle.

Relationships and Activities. None.

Funding. The study was performed with the support of the Sechenov University.

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About the Authors:
Olga V. Blagova
ORCID 0000-0002-5253-793X
Ekaterina V. Pavlenko
ORCID 0000-0002-4510-7763
Nadezhda V. Varionchik
ORCID 0000-0002-8868-0623
Vsevolod P. Sedov
ORCID 0000-0003-2326-9347
Nina V. Gagarina
ORCID 0000-0003-4575-6058
Elena A. Mershina
ORCID 0000-0002-1266-4926
Margarita E. Polyak
ORCID 0000-0003-4923-1945
Elena V. Zaklyazminskaya
ORCID 0000-0002-6244-9546
Alexander V. Nedostup
ORCID 0000-0001-9587-6707