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The connection between non-compacted myocardium layer properties and the risk of lethal outcome together with the development of thrombotic complications in children with a dilated phenotype of non-compacted myocardium: cohort study results.

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***Background**: Non-compact myocardium is a form of cardiomyopathy, which is characterized by an abnormal trabecular (non-compact) layer of the ventricular myocardium. The correlation between the severity of a non-compact myocardial layer and peculiarities of course and outcome of the disease remains unclear. **Objective**: Our aim was to examine the relationship of the ratio value of the non-compact and compact myocardial layer (NC/C) thickness, as well as of the number of non-compact segments of the left ventricle (LV) of the heart with the risk of death and thrombotic complications in children with dilated phenotype of non-compact myocardium. **Methods**: The results of a prospective cohort study, which included children hospitalized to a specialized hospital from October 2011 to May 2015, are presented. The presence of non-compact myocardium was established on the basis of echocardiography results. **Results**: The study included 48 children with non-compact myocardium and LV myocardium remodelling on the dilatation phenotype. Fatal outcome in 19 (8; 61) months from the date of detection of heart changes occurred in 11 (23%) cases. The development of thrombotic complications (cardioembolism, intravascular thrombosis before or during the observation) is recorded in 8 (17%) children. The risk of death and thrombotic complications did not depend on the NC/C value and the number of non-compact LV segments. **Conclusion**: The value of the ratio of NC/C and the number of non-compact LV myocardial segments does not allow to predict the course of the disease in children with dilated phenotype of non-compact myocardium in relation to the development of thrombotic complications and occurrence of fatal outcome.*
***KEYWORDS**: children, non-compacted myocardium, dilated cardiomyopathy, lethal outcome, thromboembolic complications.*

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BACKGROUND

Non-compact myocardium is a form of cardiomyopathy with an abnormal - trabecular (non-compact) myocardium layer in the ventricles (most frequently – in the LV apex area [1]). The right ventricle is normally more trabecular than the LV, that's why the term "non-compact myocardium" means most often the pathological changes in the LV.

The LV can be remodeled in patients with non-compacted myocardium in different ways: corresponding to dilated-, hypertrophic-, restrictive- or mixed (LV dilatation with walls hypertrophy) phenotypes [2-4]. Non-compact myocardium accompanied by various congenital cardiac defects was named non-isolated [5]. Non-compacted myocardium as a congenital condition is considered to be the result of fetal development disorders at the 2nd month of embryogenesis [1, 6, 7]. According to an alternative point of view, the disease can develop during the postnatal period [8-10].

The prevalence of non-compacted myocardium occupies the 3rd place among other cardiomyopathies [11]. The diagnosing of non-compacted myocardium has significantly increased over the recent years [3, 11, 12]. It is associated with the resolution-enhancement of the myocardium visualizing methods, which make it possible to detect the trabecular myocardium [1, 13]. Furthermore, this pathology awareness has increased in cardiologists and ultrasonography specialists [1].

The level of myocardium "non-compactness" (from small myocardium trabeculations to marked non-compacted layer) can represent a continuum – a spectrum of myocardium morphological characters [5]. However, clinical relevance of the non-compacted layer evidence and its connection with the clinical course and disease outcome remains unclear. There is no definite approach towards the interpretation of the predictive value of the NC/C ratio and its significance in selecting the patient management tactic. According to the results of a number of studies involving both children and adults, an increased NC/C ratio predicts not only LV hypo-contractility [14] but also an adverse outcome of the cardiac disease [15-17]. Similar results were demonstrated for a number of non-compacted LV segments as well [16, 18, 19]. However, a number of studies have not confirmed the predictive value of the NC/C ratio [2, 20], non-compacted LV segments quantity [2, 21] and non-compacted myocardium weight [20].

The purpose of our study was to investigate the connection between the thickness of non-compacted and compacted myocardium layers on one hand and the course of cardiomyopathy and disease outcomes on the other hand in children.

METHODS

STUDY DESIGN

A prospective cohort study was conducted.

ACCEPTANCE CRITERIA

The sample was formed from patients who were hospitalized with dilatation cardiomyopathy, an assumption of non-compacted myocardium, congenital cardiac defects and carditis.

Inclusion criteria:

1. Age under 18 years;
2. Signs of non-compacted myocardium (according to T.K. Chinn [22] and R. Jenni [23]) at ultrasonography

- 2-layer LV myocardium structure, consisting of endothelium-lined non-compacted layer (many trabeculations, separated by lacunas and communicated with the LV cavity) and underlying compacted myocardium layer with a homogenous structure;
- NC/C ratio higher than 2 (measured in end-diastole along the LV short axis or from the four-chamber view);
- Filling intertrabecular recesses with LV blood and visualized perfusion in the persisting sinusoids at color Doppler analysis;

3. Myocardium remodeled according to the dilatation phenotype.

Patients with accompanying cardiac pathology leading to an increased post-burden onto the LV myocardium, patients with accompanying storage diseases and those previously professionally doing sports were not included into the study.

STUDY CONDITIONS

The study was conducted at the cardio department of the Scientific center of children's health (SCCH, Moscow) over the period from October 2011 to May 2015. During the observation course all patients received complex symptomatic treatment of chronic cardiac insufficiency [24]. The therapy plan was picked up during the initial hospitalization and corrected over the course of future hospitalizations taking into account the patient's condition and weight, the results of examinations and the response to previous treatment.

STUDY OUTCOMES

The primary ending point of the study was the lethal outcome. Additionally we analyzed the risk of developing thrombotic complications (cardioemboly, intravascular thrombosis).

METHODS OF REGISTERING OUTCOMES

Cases of death that happened outside the SCCH (n = 8) were registered based on the information provided by the parents of the patients. In cases of information absence, we contacted the local pediatrician who observed the child, or sent a request for medical documentation to the medical institution where the patient was examined.
Trombosis cases were recorded at echocardiography (echoCG) during observation at the SCCH. Also we took into account the directions to similar complications which happened prior to hospitalization or during the period between admissions to the SCCH (according to medical documentation, delivered by the local medical institution). At the time of inclusion into the study, part of the patients were at second examination at the SCCH. In these cases, the required information was obtained from the previous histories (Jan 2005 – Sept 2011).

Echocardiographic investigation

All patients received echoCG at every hospitalization with the following ultrasonic machines: Sequoia 512 (Acuson, USA), Prosound SSD-5500 SV (Aloka Japan), Sonos-5500 (Philips, USA), Aplio XG (Toshiba, Japan), all equipped with sectoral sensors working in the frequency ranges between 3.0 and 6.5 Mhz. The number of non-compact myocardium segments of the LV was evaluated within the standard 16-segment LV model. The LV myocardium segment with the thickest wall was used in order to measure the proportion between the thickness of the non-compact and compact layer (NC/C) at the end of the diastole along the short axis of the LV or in a four-chamber position.

ETHICAL EXPERTISE

The study was approved at the joined session of the Scientific council and the Local ethical committee of the SCH (protocol #13 from 22.12.2011).

STATISTICAL ANALYSIS

The required sample size was not preliminarily calculated. Statistical analysis was performed using SPSS software v. 20 (IBM, USA). The normality of the quantitative trait values distribution was checked using the Shapiro-Wilk test. The quantitative traits description is performed in the form of the median (25th, 75th percentiles). The patients' survival rate's function is evaluated using the Kaplan-Meier curve. The Cox regression method was used to evaluate the effect of independent variables on the survival rate's function. In the first stage of the analysis the impact of each factor was assessed (univariate analysis); in the second - a multivariate analysis was performed, including only those factors for which there was a statistically significant effect on the survival rate in a multivariate analysis.

RESULTS

THE STUDY PARTICIPANTS

48 children with dilated phenotype of non-compacted myocardium were included in the study. In 12 (25%) cases, the non-compacted myocardium was diagnosed in the period from 2005 to 2009; in 36 (75%) cases - in the period from 2010 to 2014. Table 1 shows the qualitative and quantitative indicators characterizing the sample.

Table 1. Indexes, analyzed in the study

Index	Value
Girls, abs. (%)	20 (42)
Age at the time of the first hospitalization, months	57 (12; 118)
Age of detecting changes in the heart, months	13 (3; 70)
Signs of the heart failure at the time of the disease detection, abs. (%)	27 (56)
Burdened heredity*****:	
- Dilated cardiomyopathy, abs. (%)	2 (9)
- Non-compacted myocardium, abs. (%)	4 (18)
The ratio of the NC/C thickness of the myocardium	4,7 (3,8–5,3)
The number of non-compact myocardial segments	6 (4–8)
Echocardiographic parameters of LV:	
- EDD******	140 (128; 162)
- ESD******	181 (153; 217)
- the posterior wall thickness******	126 (114; 194)
- IVS thickness******	115 (101; 143)
- - Myocardial mass index, g/m^2	137 (120; 165)
ejection fraction, %	35 (29; 45)

Note. ***** — on the basis of the echocardiography results of the patient's family (data for 22 patients; in 19 cases both parents did the echocardiography, in 3 cases – only one parent); ****** — values of the indexes (the echocardiography results in NCCH) are specified in % of the values calculated by regression equations [25]; EDD — end-diastolic dimension, ESD - end-systolic dimension, IVS - interventricular septum.

Changes in the cardiovascular system in patients were first discovered in the average after the first year of life. At the same time every 4th patient's changes of heart were found during the echocardiography in the absence of clinical manifestations of the disease. In other cases,

the disease made its debut with severe symptomatic of decompensated congestive heart failure. Hospitalization in NCCH took place in an average of 7 (3; 36) months after the first symptoms.
In 12 (25%) children, an uninsulated form of a non-compacted myocardium was diagnosed. Among the associated congenital heart diseases, there were diagnosed (on 1 case): Ebstein's anomaly, mitral valve insufficiency, abnormal mitral valve's arcade and "parachute" mitral valve, hypoplasia of the left ventricle, and interatrial communication. Open aortic flow was detected in 3 children (including 1 patient with coronary-left ventricular fistula); ventricular septal defect - in 4 children.
During the NCCH's observation, patients received the following drugs: cardiac glycosides — 34 (71%), ACE inhibitors — 41 (85%), diuretics — 42 (88%), β- adrenoblockers — 33 (69%), antiarrhythmics — 17 (35%) patients. Anticoagulant therapy (antiplatelet agents, anticoagulants) was prescribed to 39 (81%) children.

KEY FINDINGS

The lethal outcome was registered in 11 (23%) cases; the median of period from the moment of the disease detection until death was 19 (8; 61) months. In 3 cases, the results of pathomorphological studies were obtained: the diagnosis of non-compacted myocardium was confirmed.
The cumulative five-year survival rate from the time of the disease detection (debut), taking into account the censor data, was 80.9%; ten-year survival rate — 75.5%. The period of observation was more than 60 (n = 17) and 120 (n = 8) months. The curve of the cumulative survival rate of patients with non-compacted myocardium depending on the disease period's duration is shown in **Fig**.

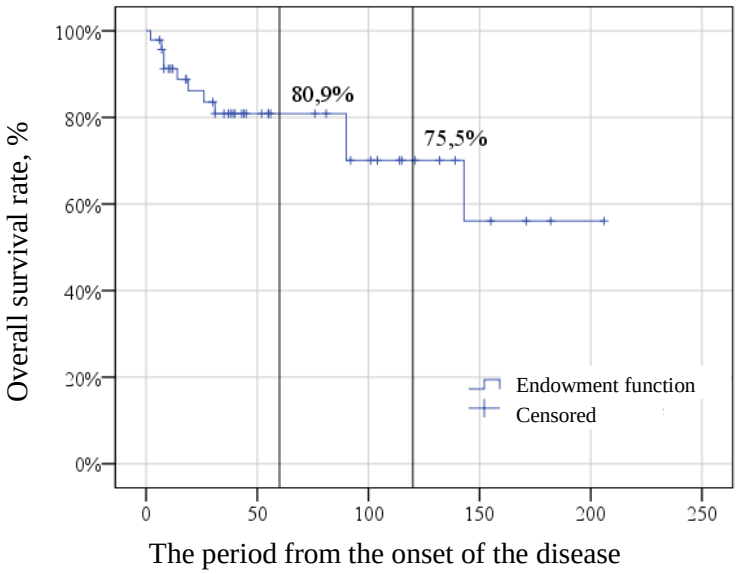

Fig. The curve of the cumulative survival rate of patients with non-compacted myocardium.

In the study of the factors that have prognostic significance, the survival rate analysis of patients with non-compacted myocardial was performed using the Cox regression method. The regression model, obtained by exclusion of irrelevant factors, did not include the ratio of NC/C and the number of non-compacted segments. The indicated factors were excluded when constructing the regression model as insignificant. Table 2 shows the value of the odds ratio for all the analyzed factors on the stage of uni- and multivariate analysis.

Table 2. Analysis of the impact of various factors on the survival rate

Factor	The odds ratio, univariate analysis		The odds ratio, multivariate analysis	
	OR	95% CI	OR	95% CI
Female	2,219	0,646–7,626	–	–
Age of the changes in the heart detection	1,014	1,003–1,024	1,019	1,004–1,033
Heart failure at the time of the changes in the heart detection	3,029	0,653–14,063	–	–
Age at the time of the first hospitalization	1,000	0,991–1,010	–	–
Non-compacted myocardium form*	4,011	1,311–4,585	4,025	2,68–4,814
The duration of observation in NCCH	0,925	0,853–1,004	–	–
The ratio of NC/C	1,046	0,605–1,806	–	–
The number of non-compact segments	0,862	0,644–1,154	–	–
Echocardiographic parameters of LV:				
- EDD**	1,017	0,996–1,037	–	–
- ESD**	1,012	0,999–1,025	–	–
- the posterior wall thickness**	0,995	0,985–1,006	–	–
- IVS thickness**	0,982	0,946–1,019	–	–
- Myocardial mass index, g/m^2	1,000	0,980–1,021	–	–
ejection fraction, %	0,889	0,813–1,973	–	–
Thrombosis in the history / in the period of observation	2,765	1,804–9,505	2,733	1,688–6,854

Note. ***** — Unisolated form of non-compacted myocardium. ** — values of the indexes (the echocardiography results in NCCH) are specified in % of the values calculated by regression equations.

ADDITIONAL FINDINGS

Formation of blood clots is registered in 8 (17%) patients; in 5 of them it was registered during the echocardiography in NCCH, and in 3 – during the survey by place of residence prior to hospitalization in NCCH. In 7 cases, the blood clots were located intracardiac (in the cavities of the LV, the right ventricle, and right atrium); 1 patient was diagnosed with pulmonary artery embolism.

During the regression analysis, the connection of the NC/C ratio and the number of non-compacted myocardium segments with the thrombosis development in children with dilated phenotype of non-compacted myocardium has not been established (Table 3). However, it was shown that the likelihood of thrombosis was higher in children with the late disease detection.

Table 3. Analysis of the impact of various factors on the incidence of thrombosis

Indicators	OR	95% CI
Child's gender	2,534	0,404–12,334
Age of the changes in the heart detection	1,015	1,001–1,037
Heart failure at the time of the changes in the heart detection	1,662	0,320–8,641
Age at the time of the first hospitalization	0,996	0,98–1,011
Non-compacted myocardium form*	0,367	0,042–3,164
The ratio of NC/C	0,883	0,368–2,003
The number of non-compact segments	0,788	0,527–1,165

Echocardiographic parameters of LV:		
- EDD**	1,017	0,990–1,048
- ESD**	1,012	0,995–1,031
- the posterior wall thickness**	0,989	0,972–1,009
- IVS thickness**	0,952	0,865–1,048
- Myocardial mass index, g/m^2	0,976	0,871–1,064
ejection fraction, %	0,903	0,795–1,012
The duration of observation in NCCH	0,973	0,869–1,011

Note. * — Unisolated form of non-compacted myocardium. ** — values of the indexes (the echocardiography results in NCCH) are specified in % of the values calculated by regression equations.

DISCUSSION

SUMMARY OF THE KEY RESEARCH FINDING

No relation has been found between the NC/C ratio and the number of non-compacted myocardium segments and disease outcome together with the risk of thrombotic complications in children with dilated phenotype of non-compacted myocardium.

DISCUSSION OF THE KEY FINDINGS

As part of our research, the course peculiarities of dilated phenotype of non-compacted myocardium in the pediatric population were studied. The impact of echocardiographic characteristics of a non-compacted myocardium on the disease symptoms and prognostic role of these factors in relation to lethal outcome were also studied. According to our data, currently, this is the most major study of non-compacted myocardium in the population of children living on the territory of the Russian Federation

In most of the messages on the non-compacted myocardium's curse in children in specialized hospitals, mortality rate is high and varies from 7 to 20% [3, 26, 27]. When selecting groups with different types of myocardial remodeling, in patients with the non-compacted myocardium, mortality in children with dilated or mixed phenotype with evidence of dilation is significantly higher than in ones with hypertrophic phenotype or normal morphometric cardiac parameters [3, 4]. Thus, according to J.L. Jefferies et al., a five-year mortality / transplant rate for the dilatated phenotype was 43% [4]. In S.T. Brescia et al.'s publication, the cumulative 5-year survival rate of patients with dilated phenotype of non-compacted myocardium was 63% [3]. In our study, the cumulative survival rate was slightly higher: it was 80.9%.

The non-compacted myocardial layer's characteristics' research results are inconsistent. According to D. Aras et al., who studied 67 adult patients, the ratio of NC/C and the number of non-compact segments had a prognostic role in relation to the development of systolic dysfunction [14]. However, in a larger G. Fazio et al.'s study of 238 adult patients with non-compacted myocardium, the influence of non-compacted segments on the development of systolic dysfunction was not detected [21]. S. Dellegrottaglie et al. analyzed the results of magnetic resonance imaging of the heart in 16 patients with non-compacted myocardium and concluded that the level of NC/C in each segment affects directly the degree of systolic dysfunction at the regional level; at the same time, the global systolic dysfunction predictor is the number of affected segments [28]. In the healthy population study, a larger myocardial trabeculation corresponded to a decrease in left ventricular function [29], which can be explained both by a direct impact of the myocardial trabecular layer on contractile function of the heart, as well as by the technical features of the LV ejection fraction's determination subject to elevated myocardial trabeculation. In our study, the NC/C ratio had no effect on the LV dimensions in both phases of the cardiac cycle, as well as on the ejection fraction, measured during the first hospitalization. Similar findings of no correlation between the NC/C ratio and ejection fraction were demonstrated by E.N. Arkhipova on 18 patients with

non-compacted myocardium [30]. Our statistical analysis has shown no relation between the characteristics of a non-compacted myocardial layer with the risk of lethal outcome.
Perhaps such differences in existing studies can be explained by the Y. Lixue et al.'s assumptions [31]. The authors believe that the data's on the prognostic role of non-compacted myocardial layer's characteristics inconsistency indicates that the LV's systolic dysfunction not only depends on the number and location of non-compacted segments, but is more closely related to the severity and the specific location of the abnormal myocardial architectonics and to the electromechanical activation in each the involved segment
One of the typical complications of non-compacted myocardium in adult population is thromboembolic conditions [32]; in pediatric studies they occur less frequently [26, 33]. The frequency of thrombosis in our study was high and amounted to 16,7% (n = 8). Both the reduced systolic function of the heart and the expansion of its cavities subject to cardiomyopathies lead to the blood flow's deceleration in the heart and in the peripheral vessels, which is a strong factor predisposing thrombus formation. The activation of neuroendocrine factors, chronic oxidative stress and pro-inflammatory changes, noted in patients with chronic heart failure, affects the rheological properties of blood [34]. It is suggested that subject to the non-compacted myocardium, the turbulent blood flow and areas of stagnation of blood in the ventricles, caused by abnormal trabeculae, can additionally predispose the thrombosis [22]. However, we found no relation of the maximum NC/C ratio, as well as the number of affected segments, with the risk of thrombotic complications.

LIMITATIONS OF THE STUDY

The study included relatively severe patients hospitalized in the central specialized hospital. This could affect the assessment of risk of death and the list of the detected risk factors for its occurrence. At the same time, the curse of non-compacted myocardium with normal function of the heart, as well as with hypertrophic and restrictive phenotypes, was not a subject of study in this work. It is necessary to emphasize the lack of consensus on the diagnostic criteria of a non-compacted myocardium. For this reason, the pathology, analyzed in various studies, can be a source of various conclusions about the outcomes of the disease in children with non-compacted myocardium.

CONCLUSION

Morphology of the myocardium's trabecularity is a spectrum of morphological traits — from minor trabeculae to severe non-compacted myocardium. We have not confirmed the prognostic importance of the NC/C value, and of the number of non-compacted myocardial segments in respect of lethal outcome in children with dilated phenotype of non-compacted myocardium. We also have not detected any relation between the NC/C ratio and the number of segments with non-compacted myocardium with the risk of thrombus formation. In this regard, these indicators cannot be used when deciding on the need for the anticoagulation therapy appointment. The mechanism, underlying the detectable thrombotic complications in case of non-compacted myocardium, requires further study.

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Conflict of interest

The authors declared they have no competing interests to disclose.

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