Impairment of myocardial perfusion correlates with heart failure severity in patients with non-compaction cardiomyopathy

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ABSTRACT

Aims Non-compaction cardiomyopathy (NCM) is a congenital heart disease characterized by an arrest of the myocardial compaction process. Although NCM patients have impaired formation of microvasculature, the functional impact of these changes remains undefined. We sought to analyse a potential correlation between myocardial ischemia and heart failure severity in NCM patients.

Methods and results We enrolled 41 NCM patients (28 male and 13 female), aged 21–70 years. In all patients, we have determined left ventricular end-diastolic volume (LVEDV), left ventricular ejection fraction (LVEF), and global longitudinal strain (GLS) by echocardiography. At the same time, serum levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) have been measured, and myocardial single-photon emission computed tomography at rest and on stress was used to define significant myocardial ischemia defined as summed difference score ≥ 2. Myocardial ischemia has been demonstrated in 11 patients (27%, Group A), and 30 patients showed no significant ischemic changes (73%, Group B). The groups did not differ in sex, age, kidney, or liver function. When compared with Group B, Group A had significantly lower LVEF (35 ± 15% in Group A vs. 53 ± 11% in Group B, P < 0.001), higher LVEDV (188 ± 52 mL vs. 136 ± 52 mL, P = 0.007), lower GLS (–9.9 ± 5.2% vs. –14.5 ± 4.1%, P = 0.001), and higher NT-proBNP levels (1691 ± 1883 pg/mL vs. 422 ± 877 pg/mL, P = 0.006). Overall, higher summed difference score was associated with lower LVEF (r = –0.48, P = 0.001), higher LVEDV (r = 0.39, P = 0.012), lower GLS (r = 0.352, P = 0.024), and higher levels of NT-proBNP (r = 0.66, P < 0.001).

Conclusions The presence of myocardial ischemia in patients with NCM is associated with worse left ventricular function, dilation of the left ventricle, and more pronounced neurohumoral activation.

Keywords Heart failure progression; Myocardial ischemia; Non-compaction cardiomyopathy

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Introduction

Non-compaction cardiomyopathy (NCM) is a rare congenital myocardial disorder that results as an arrest of myocardial compaction process in the early embryonic period. The myocardium is formed into two distinct layers—the compacted and non-compacted layer, the latter characterized by prominent myocardial trabeculations and deep intertrabecular recesses.¹⁻³ The myocardial compaction process is thought to be responsible also for the formation of coronary microvessels, as prominent trabeculations in NCM have been shown not to communicate with coronary circulation.⁴ The cardiomyocytes in non-compacted areas are therefore nourished only by diffusion from the ventricular cavity, leading to intramural perfusion.⁵⁻⁷ Often, NCM can be associated with congenital heart disease, arrhythmias, and...
neuromuscular disorders; however, isolated NCM as a primary myocardial disease has been described. Clinical manifestations of NCM are quite diverse; whilst others show signs of congestive heart failure, arrhythmias, or thromboembolisms; sudden cardiac death has been described as the first clinical manifestation also in the absence of impaired left ventricular size or function. Most patients, diagnosed with NCM, will develop symptoms of ventricular failure over the years, and as much as 47% of adults (and 75% of symptomatic patients) die within 6 years of the presentation. Guideline-based treatment of chronic heart failure with angiotensin-converting enzyme inhibitors or sartans, beta-blockers, and, in case of reduced left ventricular ejection fraction, mineralocorticoid receptor antagonists should be initiated; however, no studies have shown significant improvement of NCM patients. The origin of dysfunction remains undefined, but it is thought that microcirculatory dysfunction of trabeculated regions, leading to possible myocardial ischemia, is the key to these symptoms. Based on this hypothesis, the aims of this study are (I) to evaluate the incidence of myocardial ischemia in pathogenesis of NCM and (II) to correlate the extent of myocardial ischemia with heart failure severity.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Patient population

This prospective observational study was conducted at the Advanced Heart Failure and Transplantation Programme on Department of Cardiology at University Medical Centre Ljubljana between February 2015 and December 2018.

Patient inclusion criteria consisted of the following: age of 18–70 years, diagnosis of NCM on echocardiography, and confirmation by cardiac magnetic resonance imaging; all patients have met diagnostic criteria for NCM (end-diastolic ratio between non-compacted and compacted layers greater than 2.3). An exemplary patient with echocardiographic and MRI signs of NCM is presented in Figure 1. Exclusion criteria consisted of proven coronary artery disease either by coronary angiography or computed tomography angiography, associated congenital heart disease, and pregnancy. Informed consent was obtained from all subjects before imaging studies.

Figure 1 Images from an exemplary patient with isolated non-compaction cardiomyopathy. Images from echocardiography (ECHO; A) and cardiac magnetic resonance imaging (cMRI; B) show enlarged left ventricle with abundant trabeculations of the lateral and inferior wall. In those areas, reduced global longitudinal strain (GLS) has been observed (C). Single-photon emission computed tomography (SPECT) has shown signs of myocardial perfusion abnormalities and ischemia in described areas, as well as in antero-apical areas with no signs of trabeculations (D).
consent was obtained in all patients before participation in the study, and the study protocol was approved by the National Ethics Committee of the Republic of Slovenia (No: 21/02/15).

Study design

After enrolment, we performed a detailed clinical evaluation, transthoracic echocardiography, and myocardial perfusion single-photon emission computed tomography (SPECT) at rest and at stress and measured plasma levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Echocardiography and N-terminal pro-B-type natriuretic peptide measurements

The echocardiography data were recorded on a General Electric Healthcare Vivid E95 ultrasound system (Chicago, IL, USA) and analysed by the independent echocardiographer at the end of the study. Left ventricular end-diastolic dimension (LVEDD) and end-systolic dimension (LVESD) were measured in the parasternal long-axis view. Left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), and left ventricular ejection fraction (LVEF) were estimated using the Simpson biplane method. Two-dimensional speckle tracking echocardiography was performed measuring global longitudinal strain (GLS) and reported using the 17-segment model. All echocardiographic measurements were averaged over 5 cycles.

All NT-proBNP assays were performed at a central independent laboratory using a commercially available kit (Roche Diagnostics, Mannheim, Germany).

Myocardial perfusion single-photon emission computed tomography

Myocardial perfusion data were recorded and analysed by two experienced nuclear cardiologists, who were blinded to clinical and echocardiographic data. All patients were assigned to a two day stress/rest protocol. Technetium-99m tetrofosmin (Myoview, GE Healthcare, Chicago, IL, USA) 600 MBq was injected during exercise testing, or, when inadequate because of patient stress intolerance, additional pharmacological stress testing with regadenoson (Rapiscan, GE Healthcare, Chicago, IL, USA) 400 μg i.v. SPECT imaging was initiated 45–60 min after radioisotope injection on a dual-head gamma camera system (Siemens Symbia TruePoint SPECT-CT, Siemens Healthineers AG, Erlangen, Germany). Resting imaging was performed on the second day with the same radioisotope. Perfusion data were reported using the 17-segment model, and perfusion abnormalities were quantified with summed scores.15 Difference between summed scores on exertion and at rest yielded summed difference scores (SDSs); a SDS score of 2 or more represented myocardial ischemia. Stress testing, image acquisition, reconstruction, interpretation, and reporting were done according to the European Association of Nuclear Medicine guidelines.15

Statistical methods and analysis

Continuous variables are presented as mean (± standard deviation), and categorical variables are expressed as the numbers and percentages. Continuous variables were explored for normal distribution with the Shapiro–Wilk test. Differences within the groups were analysed using a t-test for continuous variables with correction for unequal variance when appropriate and with the χ² or Fisher exact test when appropriate. Differences between Group A and Group B were analysed with one-way analysis of variance (ANOVA). Statistical significance was assumed for ρ-values of <0.05. All statistical analyses were performed with SPSS software (Version 22.0).

Results

Patient characteristics

We enrolled 41 consecutive patients (28 males and 13 females). Based on myocardial perfusion, SPECT patients were allocated into the group with proven reversible ischemia, defined by SDS ≥ 2 (Group A) and the group with no significant reversible ischemia, defined by SDS < 2 (Group B). Groups A and B did not differ in demographic parameters, renal or liver function tests, and sinus rhythm prevalence or implantable cardioverter–defibrillator implantation rate; however, some significant differences in medical therapy were noted, mainly in antiaggregation or anticoagulation therapy. The patients in our study population had few comorbidities; only a few patients had a history of smoking or arterial hypertension; none have been diagnosed of diabetes (Table 1).

Myocardial ischemia and heart failure severity

When directly comparing the group with significant ischemia (group A) and the group with no significant ischemia (Group B), we found a significant difference within groups in LVEDD, LVEDV, LVESD, and LVESV. GLS was also found to be significantly reduced in Group A. LVEF was significantly lower in the group with proof of myocardial ischemia. We have also found significantly higher levels of NT-proBNP in Group A.
When comparing SDS and echocardiographic parameters, we found a significant correlation between SDS and LVEDD ($r = 0.43$, $P = 0.005$) and SDS and LVEDV ($r = 0.39$, $P = 0.012$). The opposite correlation was observed between SDS and LVEF ($r = -0.48$, $P = 0.001$). A significant correlation was found also in the comparison between SDS and GLS ($r = 0.352$, $P = 0.024$).

A positive and significant correlation was found in comparing SDS and NT-proBNP ($r = 0.656$, $P < 0.001$). The correlation data are presented in Figure 3.

### Discussion

To our knowledge, this is the first clinical study to date investigating clinical correlates of myocardial ischemia in patients with NCM. Signs of myocardial ischemia were found in 11 out of 41 patients; however, 30 patients showed no signs of evident myocardial ischemia.

To date, data on NCM pathogenesis are scarce and limited to few smaller studies, defining myocardial perfusion abnormalities in patients with NCM; however, possible ischemia has not been described in a larger group yet. Impaired myocardial perfusion and flow reserve in paediatric NCM cases

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### Table 1 Baseline patient characteristics

| Characteristic                  | Group A ($n = 11$) | Group B ($n = 30$) | $P$-value |
|--------------------------------|--------------------|--------------------|-----------|
| Age (years)                    | 48 ± 13            | 47 ± 15            | 0.855     |
| Male gender (%)                | 9 (82)             | 19 (63)            | 0.454     |
| Body mass index (kg/m$^2$)     | 25.6 ± 6.0         | 26.4 ± 4.2         | 0.610     |
| Sinus rhythm (%)               | 10 (91)            | 29 (97)            | 0.925     |
| ICD implanted (%)              | 7 (63)             | 23 (77)            | 0.662     |
| Sodium (mmol/L)                | 140 ± 3            | 141 ± 2            | 0.509     |
| Potassium (mmol/L)             | 4.8 ± 0.5          | 4.6 ± 0.4          | 0.217     |
| Chloride (mmol/L)              | 105 ± 5            | 105 ± 2            | 0.641     |
| BUN (mmol/L)                   | 6.0 ± 1.6          | 6.0 ± 2.6          | 0.958     |
| Creatinine (μmol/L)            | 76 ± 11            | 81 ± 26            | 0.565     |
| eGFR (mL/min/1.73m$^2$)        | 89 ± 3             | 86 ± 12            | 0.381     |
| Bilirubin (μmol/L)             | 12.4 ± 7.1         | 13.3 ± 6.5         | 0.686     |
| AST (μkat/L)                   | 0.50 ± 0.45        | 0.40 ± 0.12        | 0.299     |
| ALT (μkat/L)                   | 0.52 ± 0.23        | 0.56 ± 0.23        | 0.621     |
| AP (μkat/L)                    | 1.16 ± 0.34        | 1.03 ± 0.25        | 0.219     |
| History of smoking (%)         | 2 (18)             | 5 (17)             | 0.909     |
| History of hypertension (%)    | 0 (0)              | 4 (13)             | 0.202     |
| ACE-I/ARB (%)                  | 9 (82)             | 8 (27)             | 0.004     |
| β-blockers                     | 10 (91)            | 13 (43)            | 0.018     |
| MRA                             | 9 (82)             | 0                 | <0.001    |
| Aspirin                        | 6 (54)             | 9 (30)             | 0.281     |
| Vitamin K antagonists           | 6 (54)             | 11 (37)            | 0.303     |

ACE-I, angiotensin II convertase enzyme inhibitor; ALT, alanine aminotransferase; AP, alkaline phosphatase; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; BUN, blood urea nitrogen; eGFR, estimation the glomerular filtration rate; ICD, implantable cardioverter–defibrillator; MRA, mineralocorticoid receptor antagonist.

Values are presented as mean ± standard deviation or number of patients (percent).

### Table 2 Myocardial ischemia and heart failure progression—data

| Characteristic                  | Group A ($n = 11$) | Group B ($n = 30$) | $P$-value |
|--------------------------------|--------------------|--------------------|-----------|
| LVEDD (cm)                     | 6.3 ± 0.5          | 5.4 ± 0.8          | 0.003     |
| LVEDV (mL)                     | 188 ± 52           | 136 ± 52           | 0.007     |
| LVESD (cm)                     | 4.6 ± 0.6          | 3.5 ± 0.9          | <0.001    |
| LVESV (mL)                     | 112 ± 43           | 64 ± 32            | <0.001    |
| LVEF (%)                       | 35 ± 15            | 53 ± 11            | <0.001    |
| GLS (%)                        | −9.9 ± 5.2         | −14.5 ± 4.1        | 0.001     |
| NT-proBNP (pg/mL)              | 1691 ± 1883        | 422 ± 877          | 0.006     |
| E/Em ratio                     | 13.2 ± 12.3        | 10.2 ± 5.2         | 0.105     |

Abbreviations: E/Em ratio, ratio of the early transmitral flow velocity to the early diastolic tissue velocity; GLS, global longitudinal strain; NT-proBNP, N-terminal pro-B-type natriuretic peptide; LVEDD, left ventricle end-diastolic diameter; LVEDV, left ventricle end-diastolic volume; LVESD, left ventricle end-systolic diameter; LVESV, left ventricle end-systolic volume. Values are presented as mean ± standard deviation.
Figure 2  Myocardial ischemia and heart failure progression. When compared with Group B, Group A with proof of myocardial ischemia (A) had significantly lower left ventricular ejection fraction (LVEF), (B) larger left ventricular end-diastolic volume (LVEDV), (C) reduced global longitudinal strain (GLS), and (D) higher N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels.

Figure 3  Correlation between the extent of myocardial ischemia and heart failure severity. We have found a clear correlation between summed difference score (SDS) and left ventricular ejection fraction (LVEF; A), left ventricular end-diastolic volume (LVEDV; B), global longitudinal strain (GLS; C), and N-terminal pro-B-type natriuretic peptide levels (NT-proBNP; D).
were first reported by Junga et al.\textsuperscript{16} and was later confirmed by Jenni et al. on adult NCM patients.\textsuperscript{6} Similarly, Gao et al. recently described myocardial perfusion abnormalities, as seen by myocardial SPECT, in patients with isolated NCM; however, no correlation between the extent of myocardial perfusion abnormalities and LVEF has been observed.\textsuperscript{17} All authors speculated that myocardial perfusion abnormalities result from failure of coronary microcirculation growth and microcirculatory dysfunction.\textsuperscript{6,16,17} A recent review by Towbin et al. has also explained that the pathophysiological background of NCM could be subendocardial perfusion defects due to lack of small coronary blood vessels in the non-compacted area.\textsuperscript{3} Abnormalities were found to exist in non-compacted as well as compacted segments, suggesting that NCM is diffuse cardiomyopathy affecting also morphologically normal compacted myocardium. Compacted layer in NCM patients is however thinner and may be subject to higher wall stress, possibly provoking ischemic conditions.\textsuperscript{3,11,16}

Consistent with findings of the above trials, we were able to demonstrate myocardial perfusion abnormalities in patients with isolated NCM. Furthermore, we have also found a correlation with the extent of perfusion abnormalities and myocardial ischemia with heart failure severity, described by dilation of the left ventricle, lower LVEF, and reduced GLS as well as more pronounced neurohormonal activation assessed by serum NT-proBNP levels.

As there is no known therapy, patients with NCM often become symptomatic with signs and symptoms of advanced heart failure.\textsuperscript{5} Guideline-based heart failure therapy has been shown to have little impact on heart failure progression in NCM patients possibly leading to heart transplantation and left ventricle assist device implantation.\textsuperscript{18,19}

Patients with NCM, especially those with reduced LVEF <40\%, history of thromboembolism, or with history of atrial fibrillation, are under greater risk for thromboembolic events and should be on anticoagulation therapy with vitamin K antagonists.\textsuperscript{20} In our patient follow-up, the anticoagulation therapy has been introduced accordingly.

The data from previous studies suggest improvement of perfusion in areas adjacent to intramyocardial CD34\textsuperscript{+} stem cell injection in patients with non-ischemic cardiomyopathy.\textsuperscript{21,22} Possibly, the proangiogenic effect of CD34\textsuperscript{+} stem cell could lead to improved perfusion in ischemic areas of the left ventricle myocardium in patients also with NCM. Based on the results of our study, stem cell therapy could be associated with improvement in heart failure symptoms and LVEF, as our group has shown in a single case study.\textsuperscript{23}

**Study limitations**

The results of our study are subject to several limitations. For instance, the definition of NCM is so far not widely established.\textsuperscript{3,24} Even though our study sample size was one of the largest published so far, it was still small, with only 11 out of 41 patients with proof of ischemia. This makes the study underpowered to be definitive, and conclusions should be considered with caution.

The definition for ischemia, defined by SPECT, has been extrapolated from coronary artery disease imaging guidelines,\textsuperscript{15} even though in our patient cohort coronary artery disease has been excluded.

**Summary**

In patients with NCM, the presence of myocardial ischemia is associated with worse left ventricular function, dilation of the left ventricle, and more pronounced neurohumoral activation. Further studies are needed to investigate whether treatment approaches targeting myocardial ischemia, such as CD34\textsuperscript{+} cell therapy, may halt the progression of disease in this patient cohort.

**Conflict of interest**

None declared.

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