ESC HEART FAILURE
ESC Heart Failure 2020; **7**: 1161–1167
Published online 25 March 2020 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.12631

ORIGINAL RESEARCH ARTICLE

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

Andraz Cerar[1]*, Martina Jaklic[1], Sabina Frljak[1], Gregor Poglajen[1], Gregor Zemljic[1], Barbara Guzic Salobir[2], Maja Dolenc Novak[2], Monika Stalc[2,4], Rok Zbacnik[3] and Mirta Kozelj[4]

[1]*Advanced Heart Failure and Transplantation Programme, Department of Cardiology, University Medical Centre Ljubljana, Zaloska 7, 1525, Ljubljana, Slovenia;* [2]*Department of Nuclear Medicine, University Medical Centre Ljubljana, Zaloska 7, 1525, Ljubljana, Slovenia;* [3]*Department of Radiology, University Medical Centre Ljubljana, Zaloska 7, 1525, Ljubljana, Slovenia;* [4]*Faculty of Medicine, University of Ljubljana, Vrazov trg 2, 1000, Ljubljana, Slovenia*

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

Received: 24 October 2019; Revised: 15 December 2019; Accepted: 9 January 2020
**Correspondence to: Andraz Cerar, Advanced Heart Failure and Transplantation Programme, Department of Cardiology, University Medical Centre Ljubljana, Zaloska 7, SI-1525 Ljubljana, Slovenia. Tel: +386 41 360 543. Email: andraz.cerar@kclj.si*

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.[3,5–7] Often, NCM can be associated with congenital heart disease, arrhythmias, and

neuromuscular disorders; however, isolated NCM as a primary myocardial disease has been described.[8] Clinical manifestations of NCM are quite diverse; many patients are asymptomatic, 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.[3,9–11] 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.[7] 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.[1,12] 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.[6,13] 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.

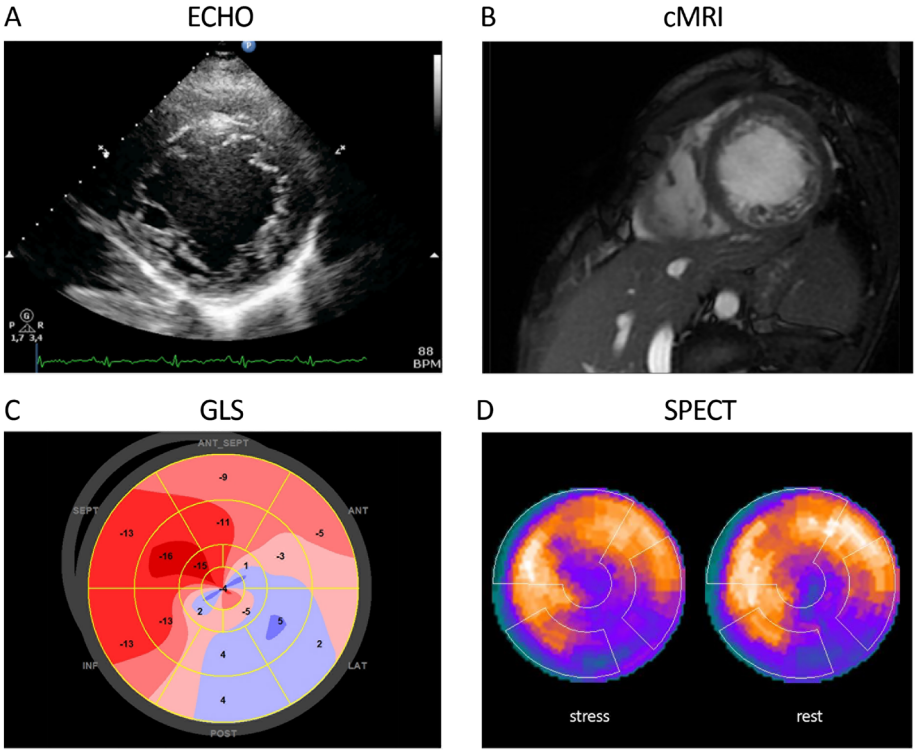
Patient population

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).[14]

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

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).



DOI: 10.1002/ehf2.12631

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 χ^2or 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 *P*-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.

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
Medical therapy			
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).

The data on group comparison are presented in *Table 2* and *Figure 2*.

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

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; LVEF, left ventricle ejection fraction; LVESD, left ventricle end-systolic diameter; LVESV, left ventricle end-systolic volume.
Values are presented as mean ± standard deviation.

DOI: 10.1002/ehf2.12631

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.

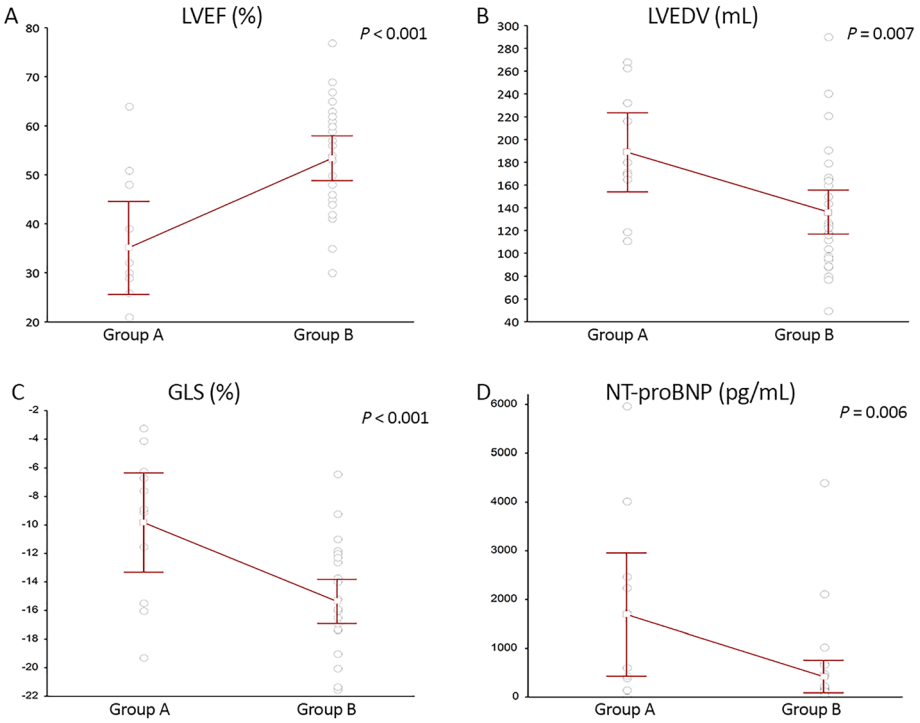
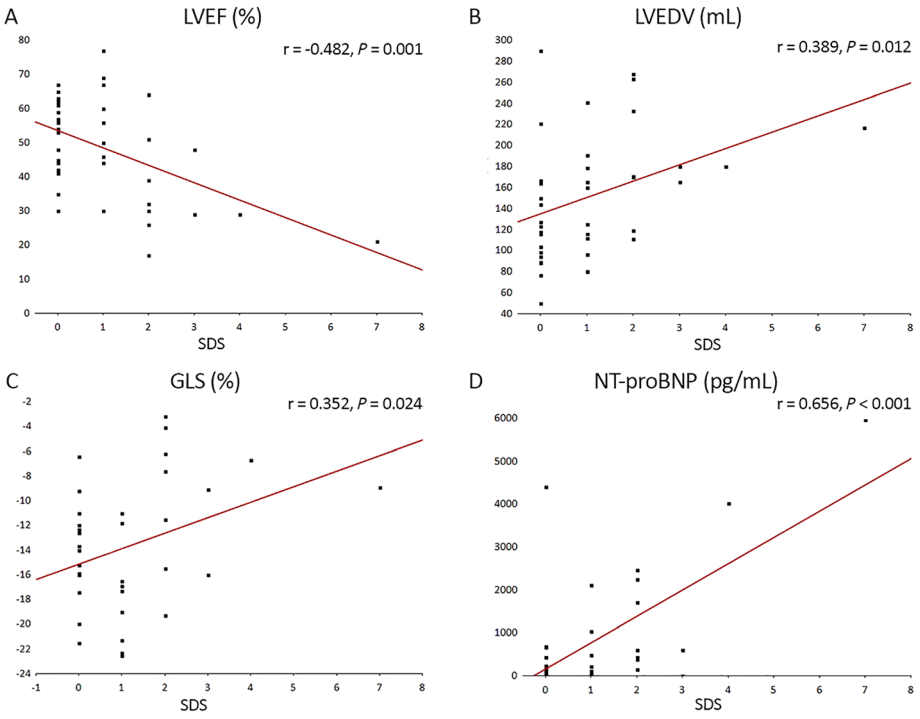


Figure 3 Correlation between the extent of myocardial ischemia and heart failure severity. We have found a clear correlation between summed difference score (SDS) and left ventricular ejection fraction (LVEF; A), left ventricular end-diastolic volume (LVEDV; B), global longitudinal strain (GLS; C), and N-terminal pro-B-type natriuretic peptide levels (NT-proBNP; D).



DOI: 10.1002/ehf2.12631

were first reported by Junga *et al.*[16] and was later confirmed by Jenni *et al.* on adult NCM patients.[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.[17] All authors speculated that myocardial perfusion abnormalities result from failure of coronary microcirculation growth and microcirculatory dysfunction.[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 noncompacted area.[3] Abnormalities were found to exist in noncompacted as well as compacted segments, suggesting than 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.[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.[4] 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.[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.[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 $CD34^+$ stem cell injection in patients with non-ischemic cardiomyopathy.[21,22] Possibly, the proangiogenic effect of $CD34^+$ 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.[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.[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,[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 $CD34^+$ cell therapy, may halt the progression of disease in this patient cohort.

Conflict of interest

None declared.

Funding

This work was financially supported by the University Medical Centre Ljubljana, Slovenia as a tertiary project.

References

1. Ritter M, Oechslin E, Sutsch G, Attenhofer C, Schneider J, Jenni R. Isolated noncompaction of the myocardium in adults. *Mayo Clin Proc* 1997; **72**: 26–31.
2. Oechslin E, Jenni R. Nosology of noncompaction cardiomyopathy: The emperor still wears clothes! *Can J Cardiol.* 2017; **33**: 701–704.
3. Towbin JA, Jefferies JA. Cardiomyopathies due to left ventricular noncompaction, mitochondrial and storage diseases, and inborn errors of metabolism. *Circ Res* 2017; **121**: 838–854.
4. Stollberger C, Finsterer J. Left ventricular hypertrabeculation/noncompaction. *J Am Soc Echocardiogr* 2004; **17**: 91–100.
5. Sedmera D, Pexieder T, Vuillemin M, Thompson RP, Anderson RH. Developmental patterning of the myocardium. *Anat Rec* 2000; **258**: 319–337.

6. Jenni R, Wyss CA, Oechslin EN, Kaufmann PA. Isolated ventricular noncompaction is associated with coronary microcirculatory dysfunction. *J Am Coll Cardiol.* 2002; **39**: 450–454.
7. Towbin JA, Lorts A, Jefferies JL. Left ventricular non-compaction cardiomyopathy. *Lancet* 2015; **386**: 813–825.
8. van Waning JI, Caliskan K, Hoedemaekers YM, van Spaendonck-Zwarts KY, Baas AF, Boekholdt SM, van Melle JP, Teske AJ, Asselbergs FW, Backx APCM, du Marchie Sarvaas GJ, Dalinghaus M, Breur JMPJ, Linschoten MPM, Verlooij LA, Kardys I, Dooijes D, Lekanne Deprez RH, IJpma AS, van den Berg MP, Hofstra RMW, van Slegtenhorst MA, Jongbloed JDH, Majoor-Krakauer D. Genetics, clinical Features, and long-term outcome of noncompaction cardiomyopathy. *J Am Coll Cardiol* 2018; **71**: 711–722.
9. Ichida F, Hanamichi Y, Miyawaki T, Ono Y, Kamiya T, Akagi T, Hamada H, Hirose O, Isobe T, Yamada K, Kurotobi S, Mito H, Miyake T, Murakami Y, Nishi T, Shinohara M, Seguchi M, Tashiro S, Tomimatsu H. Clinical features of isolated noncompaction of the ventricular myocardium: long-term clinical course, hemodynamic properties, and genetic background. *J Am Coll Cardiol* 1999; **34**: 233–240.
10. Paterick TE, Gerber TC, Pradhan SR, Lindor NM, Tajik AJ. Left ventricular noncompaction cardiomyopathy: what do we know? *Rev Cardiovasc Med* 2010; **11**: 92–99.
11. Oechslin E, Jenni R. Left ventricular noncompaction: From physiologic remodeling to noncompaction cardiomyopathy. *JACC* 2018; **71**: 723–726.
12. Li J, Franke J, Pribe-Wolferts R, Meder B, Ehlermann P, Mereles D, Andre F, Abdelrazek MA, Merten C, Schweizer PA, Becker R, Katus HA, Thomas D. Effects of beta-blocker therapy on electrocardiographic and echocardiographic characteristics of left ventricular noncompaction. *Clin Res Cardiol* 2015; **104**: 241–295.
13. Chin TK, Perloff JK, Williams RG, Jue J, Mohrmann R. Isolated noncompaction of left ventricular myocardium: a study of eight cases. *Circulation* 1990; **82**: 507–513.
14. Petersen SE, Selvanayagam JB, Wiesmann F, Robson MD, Francis JM, Anderson RH, Watkins H, Neubauer S. Left ventricular non-compaction: insights from cardiovascular magnetic resonance imaging. *J Am Coll Cardiol* 2005; **46**: 101–105.
15. Verberne HJ, Acampa W, Anagnostopoulos C, Ballinger J, Bengel F, De Bondt P, Buechel RR, Cuocolo A, van Eck-Smit BL, Flotats A, Hacker M, Hindorf C, Kaufmann PA, Lindner O, Ljungberg M, Lonsdale M, Manrique A, Minarik D, Scholte AJ, Slart RH, Trägårdh E, de Wit TC, Hesse B, European Association of Nuclear Medicine (EANM). EANM procedural guidelines for radionuclide myocardial perfusion imaging with SPECT and SPECT/CT: 2015 revision. *Eur J Nucl Med Mol Imaging* 2015; **42**: 1929–1940.
16. Junga G, Kneifel S, Von Smekal A, Steinert H, Bauersfeld U. Myocardial ischaemia in children with isolated ventricular non-compaction. *Eur Heart J* 1999; **20**: 910–916.
17. Gao XJ, Li Y, Kang LM, Zhang J, Lu MJ, Wan JY, Luo XL, He ZX, Zhao SH, Yang MF, Yang YJ. Abnormalities of myocardial perfusion and glucose metabolism in patients with isolated left ventricular non-compaction. *J Nucl Cardiol* 2014; **21**: 633–642.
18. Oechslin EN, Attenhofer Jost CH, Rojas JR, Kaufmann PA, Jenni R. Long term follow-up of 34 adults with isolated left ventricular noncompaction: a distinct cardiomyopathy with poor prognosis. *J Am Coll Cardiol* 2000; **36**: 493–500.
19. Cerar A, Ksela J, Poglajen G, Vrtovec B, Knezevic I. LVAD as a bridge to heart transplantation in a patient with left ventricular noncompaction cardiomyopathy and advanced heart failure. *Heart Surg Forum* 2016; **19**: 128–130.
20. Kido K, Guglin M. Anticoagulation therapy in specific cardiomyopathies: Isolated left ventricular noncompaction and peripartum cardiomyopathy. *J Cardiovasc Pharmacol Ther* 2019; **24**: 31–36.
21. Vrtovec B, Poglajen G, Lezaic L, Sever M, Socan A, Domanovic D, Cernelc P, Torre-Amione G, Haddad F, Wu JC. Comparison of transendocardial and intracoronary CD34+ cell transplantation in patients with nonischemic dilated cardiomyopathy. *Circulation* 2013; **128**: S42–S49.
22. Lezaic L, Socan A, Poglajen G, Peitl PK, Sever M, Cukjati M, Cernelc P, Wu JC, Haddad F, Vrtovec B. Intracoronary transplantation of CD34+ cells is associated with improved myocardial perfusion in patients with nonischemic dilated cardiomyopathy. *J Card Fail* 2015; **21**: 145–152.
23. Cerar A, Zemljic G, Frljak M, Jaklic M, Poglajen G, Sever M, Cukjati M, Vrtovec B. Transendocardial CD34+ Cell transplantation in noncompaction cardiomyopathy: first-in-man case study. *Cell Transplant* 2018; **27**: 1027–1030.
24. Oechslin E, Klaasen S. Left ventricular noncompaction phenotype in an integrated model of cardiomyopathy? *JACC* 2019; **73**: 1612–1615.