

# Left ventricular non-compaction – diagnostic challenges (RCD code: III-5A.1.o)

**Paulius Orda\*, Ausra Krivickiene, Tomas Lapinskas, Egle Ereminiene**

Department of Cardiology, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania

## Abstract

Left ventricular non-compaction (LVNC), or “spongy myocardium”, is a rare cardiac morphological condition detected in 0.05–0.26% of all adults undergoing transthoracic echocardiography, with an increasing prevalence in the recent years. Our clinical case of a 54-year-old asymptomatic female illustrates the importance of additional cardiovascular imaging technologies in the diagnostic work-up of the patient. The patient was referred to a cardiologist due to a left bundle branch block found on routine electrocardiogram examination. Transthoracic echocardiography did not reveal any specific changes, although a single photon emission computed tomography scan revealed a fixed myocardial perfusion defect. This defect was regarded as non-typical for inducible myocardial ischaemia and indicative of a non-specific cardiomyopathy. Further investigation using cardiac magnetic resonance imaging confirmed the phenotype of LVNC. JRC D 2018; 3 (8): 271–274

**Key words:** rare disease, cardiovascular imaging, echocardiography, cardiac magnetic resonance, electrocardiography

## Case presentation

A 54-year-old asymptomatic female was referred to a cardiologist due to left bundle branch block (LBBB) seen on routine electrocardiogram (ECG) examination (Figure 1). Her previous medical history included untreated grade I arterial hypertension without any other known cardiac or non-cardiac diseases, although her family history was positive for sudden cardiac death (mother and father at the age of 46 and 54, respectively). There were no abnormal findings on physical examination (body mass index [BMI] 22.9 kg/m<sup>2</sup>, blood pressure 122/60 mm Hg, heart rate 64 bpm, no audible cardiac murmurs).

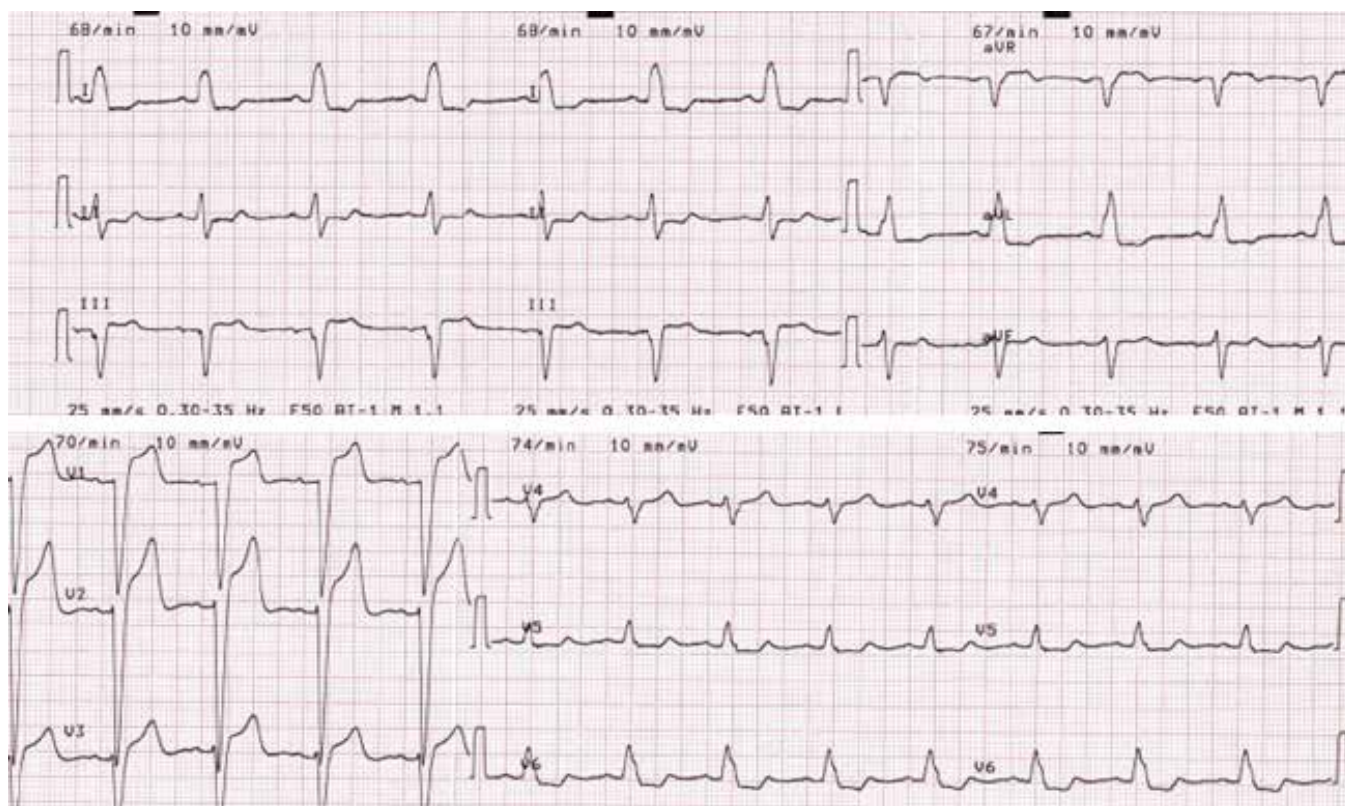
Transthoracic echocardiography (TTE) showed a mildly decreased left ventricular ejection fraction (LVEF 50%) due to asynchronous contraction induced by LBBB with no signs of valvular abnormalities. Thickness of the interventricular septum (IVS) was 10 mm, thickness of the posterior wall was 9 mm, and left ventricular end diastolic diameter (LVEDD) was 55 mm.

A single photon emission computed tomography (SPECT) scan at rest and during stress was performed in order to rule out silent myocardial ischaemia. The investigation revealed a fixed myocar-

dial perfusion defect in the anterior septal and apical segments. LVEF was 48% as calculated from gated SPECT imaging. The fixed myocardial perfusion defect was regarded as non-typical for inducible myocardial ischaemia and indicative of a non-specific cardiomyopathy.

Two years later, the TTE was repeated (Figure 2) and revealed a decreased LVEF (40%) due to hypokinesis in the apical segments of the anterolateral wall of the left ventricle (LV) and interventricular septum (due to LBBB). LV remained slightly dilated (LVEDD 54 mm, indexed LVEDD 33 mm/m<sup>2</sup>) and grade II diastolic dysfunction was confirmed. TTE did not reveal any significant changes attributable to a clear diagnosis of cardiomyopathy.

Cardiac magnetic resonance imaging (cMRI) (Figure 3) was performed for a more detailed evaluation of suspected non-specific cardiomyopathy, which revealed a decreased global EF (35%) with hypokinesis of the anterolateral wall of the LV and delayed contraction of the IVS. LVEDD was dilated – 62 mm (38.5 mm/m<sup>2</sup>), LV end diastolic and end systolic volumes were significantly increased – 193 ml (119.88 ml/m<sup>2</sup>) and 125 ml (77.64 ml/m<sup>2</sup>), respectively. Thickness of the IVS was 9 mm and thickness of the lateral wall was 7 mm. No signs of myocardial fibrosis were seen in late



**Figure 1.** ECG shows a complete left bundle branch block with a QRS duration of 142 ms

gadolinium enhancement imaging. cMRI showed that the ratio between non-compacted and normal myocardium in the anterior and lateral walls was 2.5-3. These changes confirmed the phenotype of left ventricular non-compaction (LVNC).

A 24-hour Holter monitoring test was performed to evaluate for potential rhythm or conduction abnormalities, however, no significant changes were found despite the presence of LBBB and rare premature ventricular beats.

The diagnosis of LVNC was confirmed and treatment of heart failure was initiated, which included administration of an angiotensin-converting-enzyme inhibitor (perindopril 2.5 mg once daily) and a mineralocorticoid receptor antagonist (spironolactone 25 mg once daily). Beta blockers were not tolerated due to their negative chronotropic effect. The patient has regular follow-up examinations and genetic testing is anticipated. Since the patient is asymptomatic, cardiac resynchronization therapy is currently not suggested.

## Discussion

Left ventricular non-compaction, or “spongy myocardium”, is a rare cardiac morphological condition detected in 0.05–0.26% of all adults undergoing TTE [1–3], with an increasing prevalence in recent years. A substantial proportion of healthy individuals may present with phenotypic changes of LVNC on cMRI (depending on the quantity of specific criteria for LVNC in cMRI, the frequency ranges from 1.3–14.8% of the investigated population). These findings raise a question: is LVNC a distinctive cardiomy-

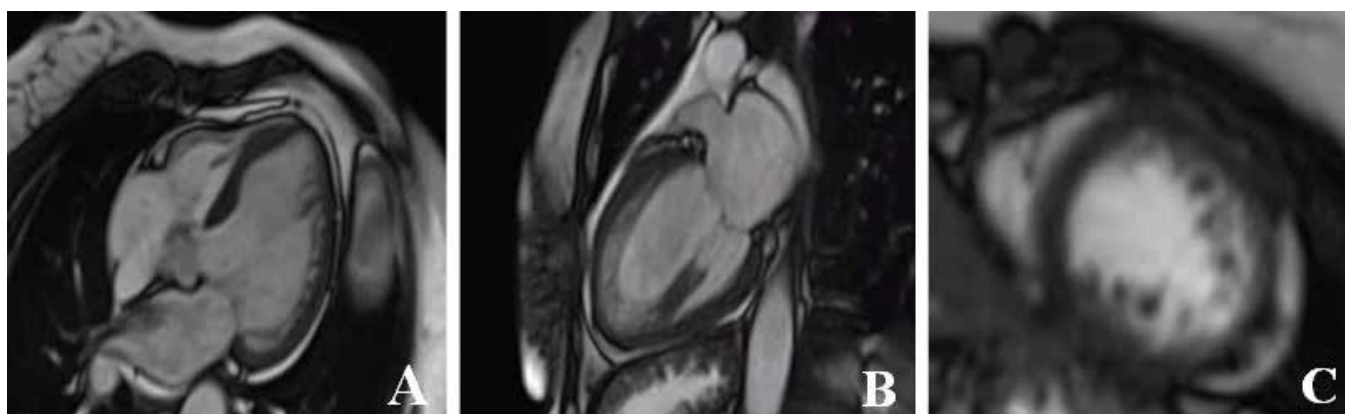
opathy (CMP) or simply a morphological phenotype of the myocardium [4–5]?

According to Arbustini et al. LVNC can present itself in three different forms and thus it may be of a different origin – it may be a) a specific trait of myocardium with normal LV size and function, b) an inherited disease associated with chromosomal anomalies, monogenic syndromes, CMP, congenital heart diseases, c) as a non-genetic LVNC observed in situations associated with a shift in loading conditions (e.g. athletes, pregnant women, sickle cell disease etc.) [6]. Towbin JA et al. have described several subtypes of LVNC: 1) benign, 2) LVNC associated with arrhythmias, 3) dilated LVNC, 4) hypertrophic LVNC, 5) restrictive LVNC, 6) right or bi-ventricular LVNC, 7) LVNC with congenital heart disease [7].

LVNC is inherited in at least 30–50% of cases, thus further genetic studies are needed [7]. It is mainly inherited in an X-linked recessive or autosomal dominant manner, although cases of autosomal recessive and mitochondrial (maternal) inheritance have been observed. Additionally, mutations do overlap. For example, the same mutation found in hypertrophic (HCM) or dilated (DCM) cardiomyopathy are found among patients with LVNC as well [4,7]. Genes associated with LVNC are associated with gene-mutations causing congenital heart abnormalities (TAZ), gene-mutations associated with sarcomeric (LDB3, MYH7, ACTC1, TNNT2, MYBPC3, TPM1, TNNI3, TAZ, LMNA) and cytoskeletal abnormalities (SCN5A, DSP). Moreover, mitochondrial genome mutations can also be associated with LVNC [7]. The MIB1 mutation has been found to cause a form of an isolated LVNC [4]. A recent study has shown that gene mutations in Lamin A/C and RBM20 carry a worse clinical prognosis compared to mutations in other genes



**Figure 2.** TTE shows mild dilation of the left ventricle. No specific changes attributable to a distinct cardiomyopathy could be outlined



**Figure 3.** Cardiac MRI reveals signs of left ventricular non-compaction: decreased EF (35%) with hypokinesis of the anterior and lateral walls of the left ventricle and tardy contraction of the interventricular septum; the ratio of non-compacted and compacted (normal) layer of myocardium is 2.5–3 at end-diastole. Myocardial non-compaction depicted in a steady-state free precession (SSFP) sequence in a (A) four chamber view, (B) two chamber view, (C) short axis view at the level of papillary muscles

such as TTN, LMNA, MYBPC3, etc. [8]. Taken together, genetic testing is very important in patients who are gene-carriers and their first-degree relatives since some genes are associated with worse prognosis and could influence the clinical decision-making process or future interventions.

Patients with LVNC can be symptomatic or asymptomatic. LV systolic dysfunction is less common among asymptomatic patients compared to symptomatic patients [9]. The presence of symptoms is associated with decreased LV systolic function, heart failure, decreased life expectancy, and increased rate of cardiovascular complications [10]. In a prospective study involving 105 patients by Habib et al., 47% of patients with newly diagnosed isolated LVNC required hospitalisation within the follow-up period of  $2.33 \pm 1.47$  years. Reasons for hospitalisation included heart failure (30%), cardiogenic shock (4%), cardiac transplantation (9%), or the patient was registered onto the transplant-waiting list (4%) [11]. Thus, decreased LV systolic function, presence of cardiovascular complications, or signs of decompensation are associated with a worse prognosis. Notably, the extent of the non-compacted zone was not predictive of death or requirement for transplantation in the French registry [11]. One study showed that the diagnosis of LVNC by any current criteria is not associated with adverse clinical events within

a 7-year follow-up period [12]. Additionally, the degree of LV trabeculation seems to have no prognostic impact over and above LV dilation, LV systolic dysfunction, and the presence of late gadolinium enhancement for the prognosis of cardiac events [13].

At present, no gold standard exists for the diagnosis of LVNC, however, the diagnosis is clinically based on criteria derived from echocardiographic and cMRI examinations. The number of trabeculae in the LV should exceed 3 and the ratio of non-compacted to compacted layers of myocardium should be  $>2:1$  at end-systole on short axis views for the diagnosis of LVNC based on echocardiographic images [14]. This ratio should be  $>2.3:1$  at end-diastole in cMRI views, although a much more specific and sensitive criterion is measuring the LV trabecular mass in short axis views, which in turn should be  $>20\%$  of the total LV mass [14]. It is important to discern LVNC from hypertrabeculation, which is often observed among patients with a long history of arterial hypertension or other long-lasting volume or pressure-associated loading conditions. These phenotypic changes of myocardial hypertrabeculation are seen among different subjects – pregnant women, athletes, patients with sickle cell anaemia, as well as among patients presenting with different forms of CMP (DCM, HCM, arrhythmogenic, restrictive) [6]. Echocardiographic strain technology is helpful in establishing

some of these diagnoses. One study demonstrated that the mid-wall strain base-apex gradient had 88.4% sensitivity and 66.7% specificity in distinguishing LVNC from DCM [15]. When differentiating between LVNC and HCM, global longitudinal strain does not appear to be an informative marker (no statistical significance, though lower values in the LVNC group), whereas an apex-base gradient with a relatively preserved apical function may be present in HCM and help in discrimination between the two pathological entities [16]. One recent retrospective study showed that among patients who were diagnosed with LVNC on cMRI, approximately one-quarter (27%) were identified as having LVNC in their echocardiography scans performed before the cMRI [17]. This fact underlines the significance of cMRI, especially when even a small suspicion of LVNC exists. Our clinical case illustrates the importance of cMRI and multimodality imaging. A computed tomography (CT) scan with contrast could be effective in the diagnosis of LVNC and can visualise trabeculae while applying the same diagnostic criteria used as for cMRI, with good specificity and lower sensitivity compared to cMRI [18,19].

The diagnosis of LVNC is based on evaluation of images derived from TTE and cMRI examinations, although additional imaging technologies may be required for a more precise analysis especially when there is uncertainty in the diagnosis, as illustrated in our clinical case. Positron emission tomography (PET) is mainly used among patients with cardiomyopathies associated with inflammation (suspicion of sarcoidosis, etc.) or CMPs of unknown origin [20,21]. The true prevalence of LVNC in PET and SPECT scans is unknown because of the non-specific pattern of the disease in these examinations. One group investigated patients with LVNC and showed that a disturbance of catabolism exists in the non-compacted segments. This study revealed that myocardial glucose uptake in non-compacted segments, when compared to the same segments in healthy individuals, is decreased, supporting the hypothesis that a cellular metabolic pathway might play a role in the pathophysiology of this disease [22]. In general, the main indication of a cardiomyopathy is an atypical pattern of myocardial perfusion and glucose uptake mismatch in PET/SPECT scans.

At present, there is no specific treatment strategy for LVNC. Mainstays of treatment include heart failure therapy, prevention of complications (mainly thromboembolic events), and adequate treatment of rhythm disturbances (emphasising the importance of proper and timely evaluation for requirement of an implantable cardiac defibrillator). Cardiac resynchronisation devices and cardiac assist devices can also be effective if clinical indications are met.

## References

- Nugent AW, Daubeney PE, Chondros P, et al. The epidemiology of childhood cardiomyopathy in Australia. *N Engl J Med* 2003; 348: 1639–1646.
- Oechslin EN, Attenhofer Jost CH, Rojas JR. 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.
- Murphy RT, Thaman R, Blanes JG, et al. Natural history and familial characteristics of isolated left ventricular non-compaction. *Eur Heart J* 2005; 26: 187–192.
- Arbustini E, Weidemann F, Hall JL. Left ventricular noncompaction: a distinct cardiomyopathy or a trait shared by different cardiac diseases? *J Am Coll Cardiol* 2014; 64: 1840–1850.
- Weir-McCall JR, Yeap PM, Papagiorcopulo C, et al. Left Ventricular Noncompaction: Anatomical Phenotype or Distinct Cardiomyopathy? *J Am Coll Cardiol* 2016; 68: 2157–2165.
- Arbustini E, Favalli V, Narula N, et al. Left Ventricular Noncompaction: A Distinct Genetic Cardiomyopathy? *J Am Coll Cardiol* 2016; 68: 949–966.
- Towbin JA, Lorts A, Jefferies JL. Left ventricular non-compaction cardiomyopathy. *Lancet* 2015; 386: 813–825.
- Sedaghat-Hamedani F, Haas J, Zhu F, et al. Clinical genetics and outcome of left ventricular non-compaction cardiomyopathy. *Eur Heart J* 2017; 38: 3449–3460.
- Lofiego C, Biagini E, Pasquale F, et al. Wide spectrum of presentation and variable outcomes of isolated left ventricular non-compaction. *Heart* 2007; 93: 65–71.
- Greutmann M, Mah ML, Silversides CK, et al. Predictors of adverse outcome in adolescents and adults with isolated left ventricular noncompaction. *Am J Cardiol* 2012; 109: 276–281.
- Habib G, Charron P, Eicher JC, et al. Isolated left ventricular non-compaction in adults: clinical and echocardiographic features in 105 patients. Results from a French registry. *Eur J Heart Fail* 2011; 13: 177–185.
- Ivanov A, Dabiesingh DS, Bhumireddy GP, et al. Prevalence and prognostic significance of left ventricular noncompaction in patients referred for cardiac magnetic resonance imaging. *Circ Cardiovasc Imaging* 2017; 10 (9).
- Andreini D, Pontone G, Bogaert J, et al. Long-term prognostic value of cardiac magnetic resonance in left ventricle noncompaction: a prospective multicenter study. *J Am Coll Cardiol* 2016; 68: 2166–2181.
- Gati S, Rajani R, Carr-White GS, et al. Adult left ventricular noncompaction: reappraisal of current diagnostic imaging modalities. *JACC Cardiovasc Imaging* 2014; 7: 1266–1275.
- Tarando F, Coisne D, Galli E, et al. Left ventricular non-compaction and idiopathic dilated cardiomyopathy: the significant diagnostic value of longitudinal strain. *Int J Cardiovasc Imaging* 2017; 33: 83–95.
- Haland TF, Saberniak J, Leren IS, et al. Echocardiographic comparison between left ventricular non-compaction and hypertrophic cardiomyopathy. *Int J Cardiol* 2017; 228: 900–905.
- Diwadkar S, Nallamshetty L, Rojas C, et al. Echocardiography fails to detect left ventricular noncompaction in a cohort of patients with noncompaction on cardiac magnetic resonance imaging. *Clin Cardiol* 2017; 40: 364–369.
- Kalisz K, Rajiah P. Computed tomography of cardiomyopathies. *Cardiovasc Diagn Ther* 2017; 7: 539–556.
- Sidhu MS, Uthamalingam S, Ahmed W, et al. Defining left ventricular non-compaction using cardiac computed tomography. *J Thorac Imaging* 2014; 29: 60–66.
- Tung R, Bauer B, Schelbert H, et al. Incidence of abnormal positron emission tomography in patients with unexplained cardiomyopathy and ventricular arrhythmias: The potential role of occult inflammation in arrhythmogenesis. *Heart Rhythm* 2015; 12: 2488–2498.
- Habib G, Bucciarelli-Ducci C, Caforio ALP, et al. Multimodality imaging in restrictive cardiomyopathies: an EACVI expert consensus document In collaboration with the "Working Group on myocardial and pericardial diseases" of the European Society of Cardiology endorsed by the Indian Academy of Echocardiography. *Eur Heart J Cardiovasc Imaging* 2017; 18: 1090–1121.
- Tavares de Melo, Giorgi MCP, Assuncao AN Jr, et al. Decreased glycolytic metabolism in non-compaction cardiomyopathy by 18F-fluoro-2-deoxyglucose positron emission tomography: new insights into pathophysiological mechanisms and clinical implications. *Eur Heart J Cardiovasc Imaging* 2017; 18: 915–921.