Challenges and diagnosis of isolated left ventricular non-compaction: A case series of 4 patients with echocardiographic diagnosis of possible ILVNC

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INTRODUCTION

Left ventricular non-compaction (LVNC) is a rare disorder that has been described as a primary genetic cardiomyopathy by the American Heart Association,[1] and an "unspecified" cardio-myopathy by the European Society of Cardiology.[2] Non-compacted myocardium can occur in association with intra-myocardial sinusoids and other complex congenital heart lesions – such as right or left ventricular flow tract obstruction, complex cyanotic heart lesions and coronary anomalies.[3,4] In contrast, isolated left ventricular non-compaction (ILVNC) is an idiopathic cardiomyopathy resulting from intra-uterine arrest of the normal myocardial morphogenesis from the epicardial to the endocardial side, in the absence of other cardiac lesions.[5] It is characterised by excessive trabeculations of the ventricular wall, with inter-trabecular recesses that are in communication with the left ventricular cavity. The excessive trabeculation of the ventricular wall is also referred to as "spongy myocardium".[4] Trabeculations have been reported in 68% of normal hearts, but these are usually three or less in number, although the diameter can be more than 2mm.[5] The age of presentation and onset of symptoms vary greatly. Patients with ILVNC usually present with heart failure, thrombo-embolism and arrhythmias – with heart failure being the most common reason for referral for echocardiography.[5]

ABSTRACT

Isolated left ventricular non-compaction (ILVNC) is a rare, congenital, idiopathic cardiomyopathy that may present in adulthood. There is no true gold standard for the diagnosis of ILVNC. Two-dimensional echo-cardiography with colour Doppler is the modality of choice to diagnose the condition. However, the diagnosis should be confirmed with cardiac magnetic resonance imaging (CMRI), as well as either a positive family history, complications of ILVNC or confirmatory genetic testing. We describe the clinical and echocardiographic features in 4 patients, each with a possible diagnosis of ILVNC, in the setting of potential alternative aetiologies for heart failure. Approval to present these cases was obtained from the institutional ethics committee and the patients also provided consent. Sufficient trans-thoracic echocardiographic (TTE) evidence of ILVNC according to previously published criteria was found in all the cases, although it was not confirmed with CMRI. This case series highlights the importance of routine echocardiography in all patients who present with heart failure – irrespective of associated risk factors. We caution against over-diagnosis of ILVNC with TTE alone, and recommend the use of CMRI as a second-line diagnostic investigation. Screening of family members and prevention of complications of confirmed cases of ILVNC are important. SAHeart 2019;16:28-34

This case series describes the clinical and echocardiographic features of patients with trabeculations consistent with ILVNC, in the setting of potential alternative aetiologies for heart failure. There are challenges and pitfalls in the diagnosis of ILVNC with transthoracic echocardiogram (TTE) as a single modality, and all suspected cases should be confirmed with cardiac magnetic resonance imaging (CMRI).

CASE REPORTS

We describe the clinical features and echocardiographic findings of 4 patients seen on referral in the period 2011 - 2014, with a possible diagnosis of ILVNC, based on the echocardiographic criteria proposed by Jenni, et al.[6] at Universitas Academic Hospital in Bloemfontein, South Africa. CMRI was not per-formed on any of these patients. Consent to publish these case reports was obtained from the patients – and the Ethics

TABLE I: Summary of patients' demographic information, and clinical and echocardiographic features.

	Age (years)	Gender	Ethnicity	Clinical and echocardiographic features
Case 1	59	Male	African	Long-standing hypertension. Presented with peripheral oedema, and class II NYHA dyspnoea.
				Echocardiography showed LV non-compaction with prominent trabeculae in the LV apex. LVEF 24%, LVEDD 7.3cm, LVESD 6.3cm
Case 2	16	Male	African	Prior diagnosis of anthracycline-induced cardiomyopathy. Asymptomatic.
				LVEF 30% with global hypokinesia and severe non-compaction of LV free wall and apex. LVEDD 6.3cm, LVESD 5.2cm.
Case 3	37	Female	African	Presented with symptoms of heart failure, 2 months post-partum, and diagnosed with post-partum cardiomyopathy.
				LVEF 18% with trabeculation of LV apex and free wall. LVEDD 5.6cm, LVESD 5.2cm
Case 4	48	Male	African	History of alcohol abuse. Presented with chest pain and palpitations, with an "irregular pulse".
				Echocardiography showed severe trabeculations from mid-to-apical region. "Smoke"* observed in LV; LVEF 24%.

*NYAH = New York Heart Association, LV = left ventricle, LVEF = left ventricular ejection fraction, LVEDD = left ventricular end-diastolic dimension, LVESD = left ventricular end-systolic dimension. *"Smoke" refers to spontaneous echocardiographic contrast (SEC).*

Committee of the Faculty of Health Sciences, University of the Free State (ECUFS 234/2015), approved publication. The patients' clinical features and demographic information are summarised in Table I.

Case 1

A 59-year-old male patient with a long-standing history of hypertension, presented with class II New York Heart Association (NYHA) dyspnoea and bilateral pitting oedema. Echocardiographic findings revealed a left ventricular ejection fraction of 24% with a markedly trabeculated left ventricle.

Case 2

A 16-year-old male patient with a history of a skin tumor as a four-year-old, and treated with an anthracycline-based regimen. He developed heart failure with reduced ejection fraction at age 5, and was diagnosed and treated as anthracycline-induced cardiomyopathy with good clinical response. He defaulted follow-up at age 12 and represented at age of 16, still asymptomatic. Echocardiography was performed showing left ventricular ejection fraction (LVEF) of 56%, and the diagnosis of ILVNC was made based on the TTE findings. His ejection fraction deteriorated over the following 3 years to 24%, with severe LVNC visible on echocardiography, as shown in Figure 1. At the most recent follow-up, he was still asymptomatic and on warfarin and anti-failure treatment.

Case 3

A 37-year-old female patient who presented with NYHA class IV dyspnoea, which started two months postpartum. She was
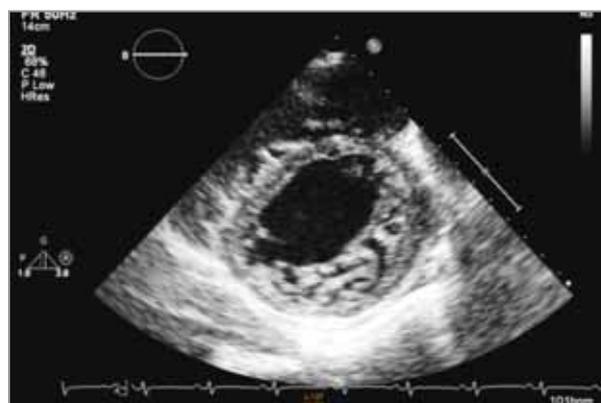

FIGURE 1: Echocardiography of Case 2.
Short-axis view showing trabeculations in the left ventricular wall, with inter-trabecular recesses in continuation with the left ventricular cavity.

FIGURE 2: Apical 4 chamber view of Case 3, showing trabeculations in the apex of the left ventricular wall.
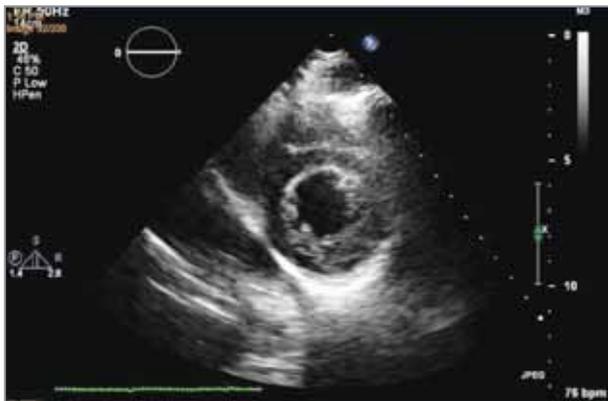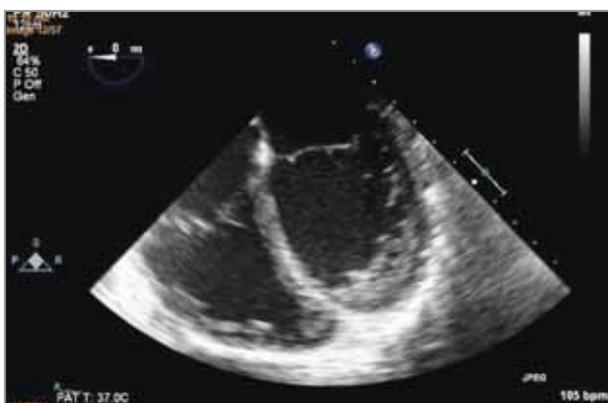
FIGURE 3: Short axis view of Case 3.

FIGURE 4: Transoesophageal echocardiogram (TOE) image of Case 3, showing trabeculations at the apex of the left ventricular wall.

referred for echocardiography due to refractory heart failure. She had no family history of cardiac disease and no features of embolic phenomena. TTE showed an LVEF of 18% with trabeculations of the apex of the left ventricle (Figures 2, 3 & 4), consistent with criteria proposed by Jenni, et al.[6] for the diagnosis of ILVNC. No thrombi were documented on echocardiography.

Case 4

A fit, 48-year-old male patient with a history of alcohol abuse, presented with typical angina chest pain and palpitations, without symptoms of heart failure. An electrocardiogram (ECG) was performed, which showed a narrow complex tachycardia, no P waves in standard lead II and V1, deeply inverted T waves in all leads, and Sokolow-Lyon voltage criteria for left ventricular hypertrophy (Figure 5). He was admitted to the coronary care unit and treated with adenosine and later intravenous amiodarone. The ECG immediately following

amiodarone showed a bigeminal rhythm with inverted T waves in all leads. Normal coronary arteries were found on angiography. He later developed sinus bradycardia with deep inverted T waves and left ventricular hypertrophy. A subsequent 24-hour holter ECG showed no dysrhythmia. Although lost to follow-up, a family member reported that he was still alive and well without treatment, and chose to terminate follow-up. His echocardiographic findings are presented in Figures 6 and 7.

DISCUSSION

During early foetal life, at approximately 5 - 8 weeks of embryonic development, the myocardium is a network of muscle fibres separated by deep recesses that are in connection with the left ventricular cavity. As embryonic life continues, the process of compaction occurs from the epicardium to the endocardium, and from the base of the heart to the apex.[4] The coronary circulation develops during the same time and the recesses are reduced to capillaries. Ventricular non-compaction is a result of altered intra-uterine compaction of the myocardium.

ILVNC can be sporadic or familial. Familial recurrence of ILVNC can be autosomal dominant, X-linked or mitochondrial in origin. Genetic heterogeneity within this disorder has been reported, and a number of mutations are recognised to cause ILVNC; however, no single gene abnormality has been described.[7] Major genetic mutations in ILVNC and their association with other cardiomyopathies have been described.[4,8] In 2013, Esposito, et al.[8] reported the first, and to our knowledge, the only case of LVNC associated with congenital fibre type disproportion (CFTD) in an Italian family. Two novel genes have been described, with their synergistic effect resulting in a severe disease phenotype.[8] Despite the fact that ILVNC is a congenital condition, it may present in adulthood.[5,9-11] It is recommended that a meticulous three-generational family history be obtained to evaluate for genetic influence, as a positive family history has an impact on screening of other family members.[12] Follow-up of family members of an index case has identified a 30% familial occurrence.[13] Between 60% and 70% of cases of ILVNC are sporadic. The Heart Rhythm Society has made a Class I recommendation that genetic testing be performed on relatives when a specific gene has been identified.[14]

There is no true gold standard for the diagnosis of ILVNC. Diagnostic criteria are still evolving and standardised diagnostic criteria have not yet been established.[7,15] It is important to note that there is a risk of over-interpretation of trabeculations
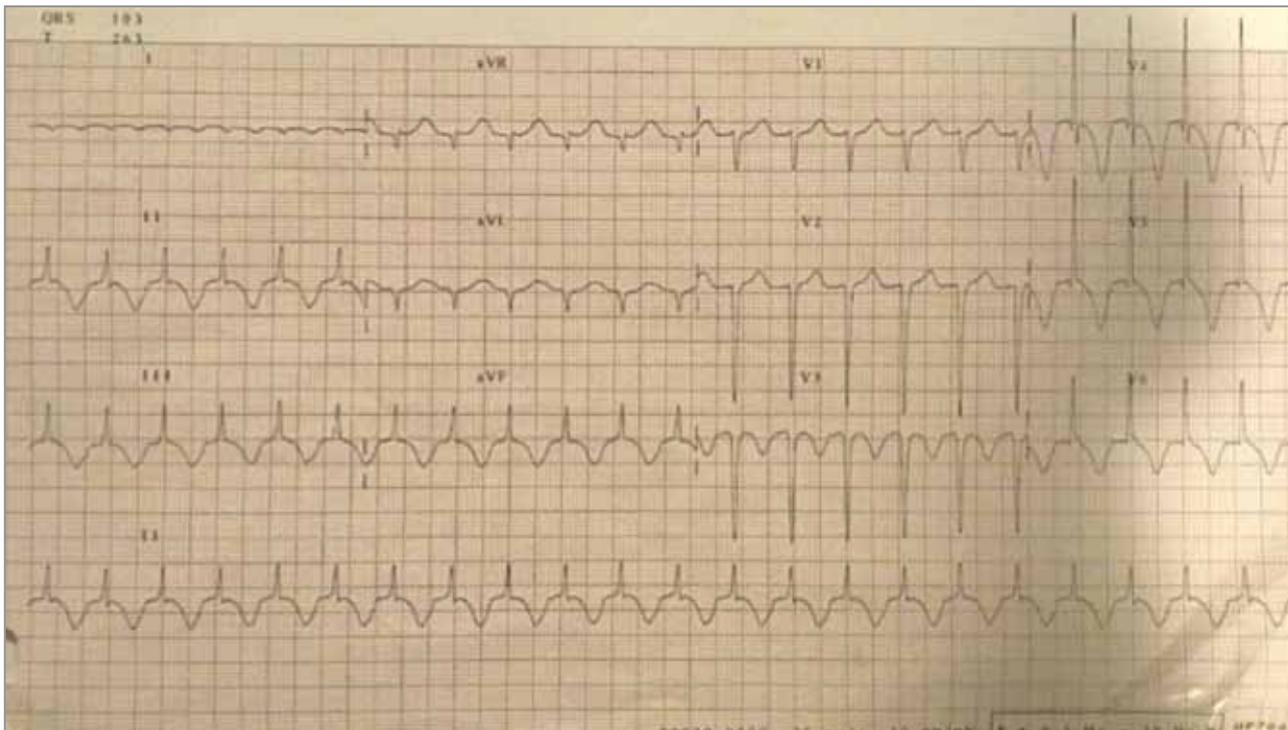
FIGURE 5: ECG findings of Case 4 at presentation.

FIGURE 6: Short-axis echocardiographic views of Case 4, showing trabeculations.
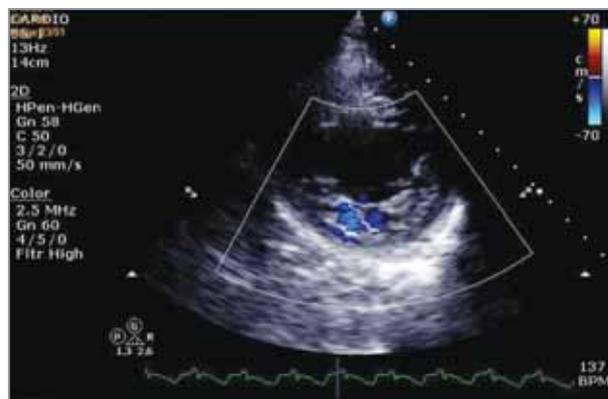

FIGURE 7: Short-axis views of Case 4, showing flow within the trabeculations from within the left ventricle.

on TTE. Prominent trabeculations may be part of normal hearts, and may be prominent in athletes and African patients. Pathological conditions such as dilated cardiomyopathy, apical hypertrophic cardiomyopathy (HCM), and peri-partum cardio-myopathy, in patients recovering from myocarditis and hyper-tensive heart disease, may mimic ILVNC. Peri-partum cardio-myopathy may be a more suitable diagnosis than ILVNC in Case 3 and Case 4, and could be apical HCM. CMRI might have been useful to differentiate ILVNC from other aetiologies of hypertrabeculation.

Compared to non-compaction, trabeculations in normal hearts run from the free wall to the septum, while in ILVNC the trabeculations do not involve the septum.[7] In dilated cardio-myopathy and hypertensive heart disease, the ratio of the trabeculated to the non-trabeculated layer is 0.8 and 1.1, respectively.[6] Normal trabeculation of the left ventricle is prominent in black African patients compared to white patients, and has the phenotypical appearance of ILVNC, without the presence of left ventricular disease.[10] Two-dimensional echo-cardiography with colour Doppler is the modality of choice

TABLE II: Echocardiographic diagnostic criteria compiled from Jenni, et al.[6]

Diagnostic criteria	Echocardiographic notes
Compacted epicardial layer and non-compacted endocardial layer with prominent trabeculae and deep inter-trabecular recesses	Short axis view; end-systole
Ratio of non-compacted to compacted layer of >2	Maximally affected segment
Segmental hypokinesia and non-compaction involving mainly the mid-lateral wall, and apical and mid-inferior wall	End-systole
Evidence of forward blood flow from ventricular cavity to inter-trabecular recesses throughout the cardiac cycle	Colour Doppler
Absence of co-existing cardiac anomalies	

TABLE IV: Criteria for diagnosis of ILVNC, as suggested by Garcia-Parvia, et al.[21]

1: Patient must fulfill quantitative short-axis diagnostic criteria on both of the following:
• Echocardiography (Jenni[6] criteria) and
• Cardiac magnetic resonance imaging (Jacquier[17] criteria)

2: Patient must have at least 1 of the following features:
• LVNC diagnosed in another family member;
• Regional wall motion abnormalities;
• ILVNC-related complications (arrhythmia, heart failure, or thromboembolism); or
• A carrier of a pathogenic mutation in a gene previously associated with LVNC in various families, or novel disease-causing mutations using next-generation sequencing techniques and validation of these mutations in experimental disease models.

TABLE III: Cardiac magnetic resonance imaging (CMRI) criteria for ILVNC.

Author	CMRI Criteria
Petersen, et al.[19]	Pathological non-compacted myocardium to compacted myocardium >2.3 during end-diastole predictive of ILVNC. (sensitivity = 86%, specificity = 99%).
Jacquier, et al.[17]	Trabeculated left ventricular mass >20% of global ventricular mass is predictive of ILVNC. (Sensitivity = 91.6%, specificity = 86.5%)

for the diagnosis of ILVNC,[16] and is considered a first-line investigation. TTE is safe, non-invasive, cost-effective and readily available in most facilities in developing countries. It is unknown which diagnostic echocardiographic (morphologic) criteria are most sensitive and specific.[15]

Echocardiographic criteria have been proposed for the diagnosis of ILVNC,[6] and our institution uses the criteria published by Jenni, at al.,[6] as summarised in Table II. The application of these echocardiographic criteria allows some differentiation between ILVNC and ILVNC mimickers. There is inaccuracy in evaluating compacted versus non-compacted myocardium with oblique image planes or off-axis images. Standard chamber views must be obtained, and contrast may be used to improve imaging of the apex.

Cardiac magnetic resonance imaging (CMRI) is a second-line investigation used to support a TTE diagnosis of ILVNC, and can better differentiate compacted and non-compacted myo-

cardium. Unlike TTE, CMRI is not dependent on specific views, and allows the whole ventricle to be visualised rather than segments. The apical, anterior, anterolateral and lateral aspects of the ventricle are better visualised using CMRI.[16,17] Specific diagnostic criteria (Table III) have been established for the diagnosis of ILVNC on CMRI.[18,19]

Despite better imaging, CMRI is not an ideal investigation; availability is limited, and it requires expertise to interpret. Furthermore, some patients may have metal implants/devices that limit CMRI use. In addition, the investigation takes time and requires a patient who can lie supine and be able to cooperate with breath-holding, which may be difficult in patients with symptomatic heart failure. False positive results may occur in asymptomatic patients.[20] Garcia-Pavia, et al.[21] have suggested that the criteria in Table 4 are applied to make a definitive diagnosis of ILVNC.

The prevalence of ILVNC is unknown, and echocardiographic studies have reported a prevalence of 0.014% - 1.3%,[7,11] and the diagnosis may often be missed. A number of cases have been reported from Africa,[9,22-26] including South Africa.[10,22] At a cardiomyopathy clinic in Johannesburg, the prevalence of ILVNC was 6.9%, and the diagnosis was based on echo-cardiographic criteria alone.[10]

The myocardial segments predominantly affected according to TTE performed in our case series, were the apex (50%) and the lateral wall (50%). None of our patients presented with inferior wall involvement, which was contrary to other published studies where the inferior wall was predominantly affected in more than 74% of cases.[3,5,10,11] This suggests that alternate

diagnoses should be considered in our patients, and supports the need for CMRI and applying the criteria proposed by Garcia-Pavia, et al.[21] (Table IV) to confirm or exclude a diagnosis of ILVNC.

The clinical presentation of patients reported ranges from asymptomatic to disabling refractory heart failure. In asymptomatic patients, non-compaction may occur as an incidental finding on echocardiography, and ILVNC may be found in patients with unexplained heart failure. Symptomatic patients with ILVNC usually present with heart failure, arrhythmias or embolic phenomena.[8]

The thrombo-embolic features in patients with NCLV can be attributed to thrombus formation in the inter-trabecular recesses, combined with the hypokinetic myocardium and systolic dysfunction. In previous studies, thrombo-embolic complications were reported at a frequency of 9% - 38%.[3,5,11,24] There is no agreement about anticoagulation therapy in patients with LVNC. Some authors favour the use of anticoagulation agents in patients with non-compaction, regardless of the patient's history of thrombosis.[3,4,6,7] Visible thrombus and atrial fibrillation are definite indications for anticoagulation. The CHADS$_2$/CHA$_2$DS$_2$-VASc score may be used in patients with reduced ejection fractions in the absence of atrial fibrillation, to guide anticoagulation in cases of confirmed ILVNC.[27]

The frequency of arrhythmias in ILVNC varies between 14% and 63% in published case series,[3,5,11,24] and occurred in 1.8% of patients with LVNC in a previous South African study.[10] The mortality rate in Oechslin's cohort[3] was 35%, with sudden cardiac death and heart failure responsible for 50% and 33%, respectively, of all deaths.[3] The histologic and autopsy findings of fibrosis and scarring can theoretically explain the arrhythmogenicity of the myocardium.[4,6]

ILVNC during pregnancy has been reported.[6] However, de novo left ventricular trabeculations may be found in a significant number of asymptomatic pregnant women as a result of increased pre-load and physiologic response to pregnancy, and then resolve later.[28] A diagnosis of ILVNC should thus not be made in the peri-partum period.

CONCLUSION

We describe 4 cases of possible ILVNC, a low prevalence disease, based on TTE findings, in the setting of alternative aetiologies for heart failure. Echocardiography is the standard test for diagnosis; however, if suggestive of ILVNC, CMRI should be performed to rule out or confirm the disease. In the case of confirmed ILVNC, genetic consultation and testing of family members are necessary.

We recommend that even in resource-poor settings such as ours, all patients presenting with clinical signs and symptoms of heart failure should be referred for TTE. However, we caution against over-diagnosis of ILVNC using echocardiographic criteria alone. African patients, athletes and peri-partum patients, may have increased trabeculations that may be physiological.

Conflict of interest: none declared.

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