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The Electrocardiogram in the Diagnosis and Management of Patients With Left Ventricular Non-Compaction

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Abstract

Purpose of the Review Left ventricular non-compaction (LVNC) is characterised by prominent left ventricular trabeculae and deep inter-trabecular recesses. Although considered a distinct cardiomyopathy, prominent trabeculations may also be found in other cardiomyopathies, in athletes or during pregnancy. Clinical presentation includes heart failure symptoms, systemic embolic events, arrhythmias and sudden cardiac death. Currently, LVNC diagnosis relies on imaging criteria, and clinicians face several challenges in the assessment of patients with prominent trabeculations. In this review, we summarise the available information on the role of the ECG in the diagnosis and management of LVNC.

Recent Findings ECG abnormalities have been reported in 75–94% of adults and children with LVNC. The lack of specificity of these ECG abnormalities does not allow (in isolation) to diagnose the condition. However, when considered in a set of diagnostic criteria including family history, clinical information, and imaging features, the ECG may differentiate between physiological and pathological findings or may provide clues raising the possibility of specific underlying conditions. Finally, some ECG features in LVNC constitute ominous signs that require a stricter patient surveillance or specific therapeutic measures.

Summary The ECG remains a cornerstone in the diagnosis and management of patients with cardiomyopathies, including LVNC.

Keywords Electrocardiogram · Left ventricular non-compaction · Cardiomyopathies · Arrhythmias · Sudden cardiac death

Introduction

Left ventricular non-compaction (LVNC) is a cardiomyopathy characterised by prominent left ventricular trabeculae and deep inter-trabecular recesses. While the European Society of Cardiology includes LVNC in the unclassified cardiomyopathies group, the American Heart Association defines LVNC as a genetic cardiomyopathy [1, 2]. The diagnosis of LVNC relies on a double-layered myocardial architecture demonstrating a non-compacted myocardium with deep trabeculations and a thin compacted epicardial layer. Imaging techniques, such as echocardiography and cardiovascular magnetic resonance (CMR) are the main diagnostic tools in this setting. The commonly used imaging diagnostic criteria are mainly based on the ratio between the non-compacted and the compacted layer of the ventricular myocardium [3]. However, there are currently no gold standard echocardiographic or CMR criteria for the diagnosis of LVNC [4]. The diagnosis of LVNC remains challenging, reflecting the lack of stringent criteria for the definition of this condition. Prominent trabeculations (the characterising feature of the disease) may be physiological in athletes or during certain stages of pregnancy or may be commonly found in other cardiomyopathies (e.g. dilated, hypertrophic, arrhythmogenic), congenital heart diseases or as part of inherited genetic

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multiorgan diseases such as Barth syndrome [4–8]. Practical consequences linked to this diagnostic variability emerge in the high prevalence of "spongy myocardium" phenotypes observed in echocardiographic laboratories or CMR units, often resulting in an overinterpretation of clinical findings that may be physiological [9]. While data from the European Cardiomyopathy Pilot Registry report LVNC prevalence of 3.2%, this prevalence is even higher (9.2%) in children according to the National Australian Childhood Cardiomyopathy Study [10, 11]. The overall prevalence of LVNC seems to be much higher when considering a specific subset of patients and certain ethnicities [3, 9, 12]. The spectrum of clinical presentation is wide, depending for example on whether LVNC occurs in isolation or in the context of a complex genetic syndrome. Overall, the clinical key features (classic triad) include heart failure symptoms (as the result of ventricular systolic/diastolic dysfunction), systemic embolic events and ventricular arrhythmias [4]. Life-threatening arrhythmias were reported in more than 20% of the patients and sudden cardiac death (SCD) is a matter of concern [4]. In this context, the electrocardiogram (ECG) may be a relevant tool in the assessment of patients with possible or ascertained LVNC. Its use may be particularly relevant in differentiating between physiological and pathological changes, but also in prognostic stratification and clinical management (Fig. 1). In this review, we will discuss the role of the ECG in the clinical approach to patients with LVNC. The ECG might be a useful tool, especially in situations where the increasing amount of information (often with findings of uncertain significance) derived from other more advanced diagnostic techniques does not provide practical support for clinical choices.

Methods

The following research question was addressed: What is the role of the ECG in the diagnosis and management of LVNC? A search through the web-based engine PubMed was conducted to identify all studies relevant to the topic. Due to the lack of studies specifically focussing on the ECG and the complexity of the disease in terms of diagnostic criteria, we considered all literature on LVNC that reported on the ECG including research papers, reviews, case series and reports. Table 1 summarises sample characteristics and key findings

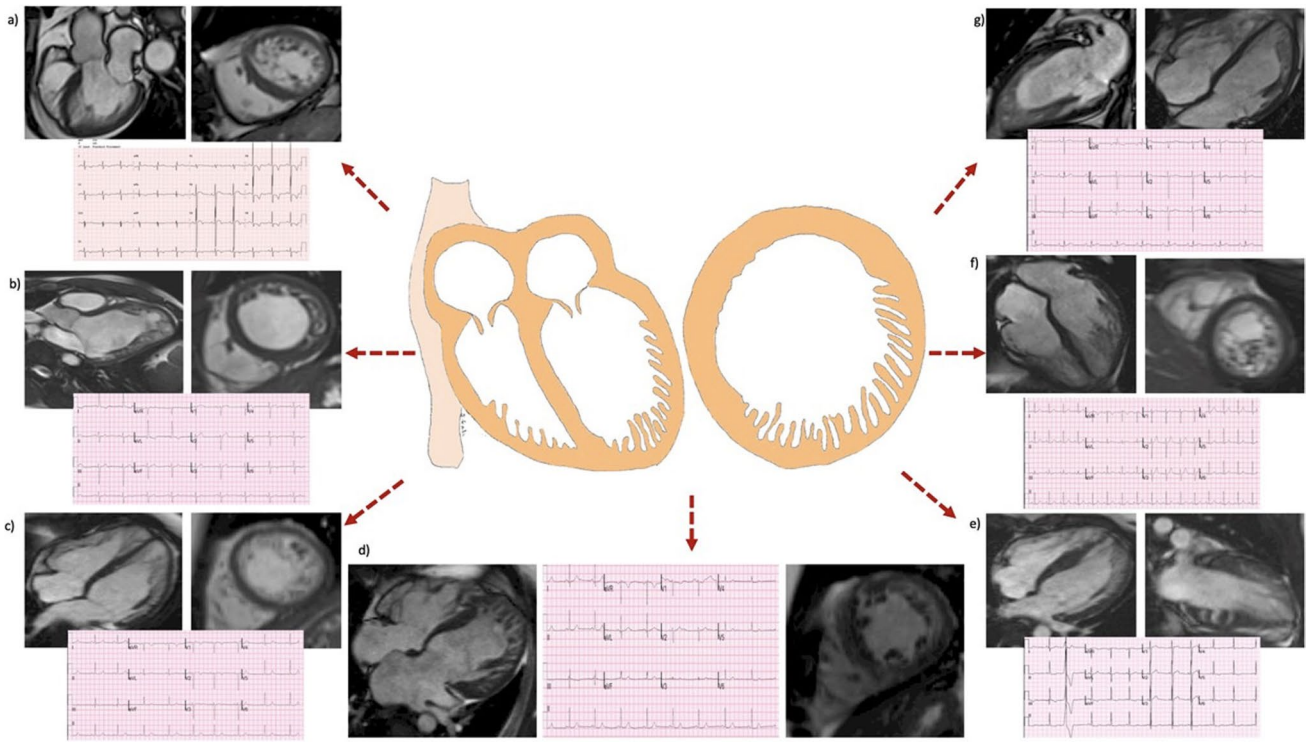

Fig. 1 Electrocardiographic abnormalities in patients with different LVNC structural phenotypes on cardiac magnetic resonance imaging. (a) ECG fulfills voltage criteria for left ventricular hypertrophy; deep T-wave inversion in leads V4–V6 with associated ST segment depression; minor T-wave inversion in leads I, II, avL and aVF; biphasic T-wave noted in lead 3 with a proceeding convex ST segment. (b) Left axis deviation with minor T-wave inversion in lateral leads (leads I, aVL, V4–V6). (c) Minor T-wave inversion in V1–V3. (d) Fragmentation of QRS morphology in leads III, V3 and V4. (e) Minor T-wave inversion in leads II, III, aVF and V4–V6. There is also an isolated ventricular extra-systole. (f) Normal ECG with no repolarization changes. (g) Deep R/S complexes in leads V2–V3

in manuscripts of particular importance that were considered in this review.

Systematic Approach in ECG Interpretation

ECG abnormalities are frequently observed in patients with LVNC, ranging from 75 to 94% in adults and children [13–20]. When interpreting the ECG, the recognition of specific "red flags" should be carefully integrated into the broader clinical and familial context (Table 2).

P Wave

Although the left ventricle (LV) is the chamber predominantly affected by LVNC, the atria may also be involved. This would be a consequence of LV involvement with diastolic dysfunction and subsequent left atrial (LA) dilatation [21]. These changes may be reflected in the ECG with broad or peaked P waves [13, 17, 22]. Sinus node dysfunction and sinus bradycardia can be the initial manifestations in some patients with LVNC [17, 23].

PR Interval

Conduction abnormalities such as first-degree and advanced atrio-ventricular (AV) block are found in a variable percentage (3–25%) of patients with LVNC [17, 19, 24]. In a study by Steffel et al., conduction abnormalities were associated with a reduced LV ejection fraction (LVEF), LV and LA dilatation and congestive heart failure (HF) [22]. Conduction abnormalities have also been observed in children with LVNC when compared to age-matched healthy individuals, with a prolonged PR interval observed in LVNC (136 ± 28 ms vs 105 ± 16 ms, $p < 0.001$) [17].

The QRS Complex

Structural abnormalities of the LV (and sometimes of both ventricles) and the possible involvement of the conduction tissue are both reflected on the QRS complex. ECG voltage criteria of left or bi-ventricular hypertrophy are reported in > 40% of patients, and extremely high QRS voltages have been described in children with LVNC [17–20, 22, 24, 25]. Steffel et al. showed a higher prevalence of systemic embolic events among patients with ECG signs of left ventricular hypertrophy [22]. In a recent bi-centric retrospective study involving 305 patients and investigating the relationships between QRS duration and left ventricular (LV) mass in subtypes of abnormal LV wall thickness for differentiation of hypertrophic cardiomyopathy (HCM) from other forms of LV hypertrophy, QRS duration increased in the subgroup ($n = 28$) of patients with LVNC (rho 0.40, $p = 0.007$ on bivariate regression between QRS duration and LV mass), while a reverse relationship was present in patients with HCM [26]. Bundle branch blocks (especially left bundle branch block — LBBB) are a common finding in adult patients with LVNC (over 40% of cases), while they are rare in children [13–17, 19]. Intraventricular conduction delay (particularly LBBB) is associated with reduced systolic function, heart failure and left ventricular dilation [15, 17]. The presence of fragmented QRS (fQRS) though non-specific has also been described in LVNC. A study by Ning et al. suggested that the presence of fragmented QRS was associated with a significantly lower survival rate [27].

ST Segment/T Wave Abnormalities

Repolarization abnormalities are reported in over 70% of all cases. The most common findings are ST-segment depression and negative or flat T waves, especially in the inferior and lateral leads [15, 17, 22]. A positive T wave in aVR lead is also commonly described (up to 40% of cases) [28•]. In a study by Caliskan et al., an early repolarization pattern was a common finding in LVNC, especially in subjects presenting with malignant ventricular arrhythmias and inferior or inferolateral pattern and horizontal/descending type seems to be associated with higher risk of poor outcomes [29]. Interestingly, a Brugada ECG pattern has been reported in 3.2% of Japanese patients with LVNC, with a significantly higher prevalence compared to the general population [30].

QT Interval

Several studies have shown that patients with LVNC may exhibit a prolonged QTc interval. Stöllberger et al. found a QTc interval > 440 ms in 38% of patients with LVNC [19]. Similarly, Steffel et al. documented a high prevalence (up to 52%) of prolonged QTc (QTc ≥ 450 ms for men and ≥ 470 ms for women) in these patients [22]. Brescia et al. found in a series of 242 patients that 22 (9%) had a prolonged QT interval (461–652 ms). The significance of prolonged QTc interval in this context is unclear [20].

VEBs

Ventricular ectopic beats (VEBs) are commonly found in patients with LVNC [31]. A study by Van Malderen et al. on 101 patients with ECG-investigated LVNC showed that VEBs were present in 54% of cases [31]. Most (95%) VEBs originated from the outflow tracts, the fascicles and the mitral and/or tricuspid annulus. Therefore, it is possible that VEBs are not causally related to the structural abnormalities typical of LVNC per se. However, a link between ventricular

Table 1 Sample characteristics and electrocardiographic findings in studies investigating LVNC

Study	Sample size	Male gender	Age	LVNC phenotype	Prevalence and type of ECG abnormalities	Key message
Caliskan K et al *J Cardiovasc Electrophysiol 2012* [29]	84	8 (57%) in the VT/VF group, 32(45%) in the other group	40 (3–79)	LVNC	Early repolarization (ER) in 25 of 64 patients (39%) without LBBB: 6% in inferior leads, 27% in lateral leads, and 15% in both	High prevalence of ER in patients with LVNC, especially in those with malignant ventricular arrhythmias
Cetin MS et al *Am J Cardiol 2016* [80]	88	64.8%	38.6 ± 17.7	LVNC	fQRS in 53.4%	fQRS predictor of arrhythmic events and cardiovascular mortality in patients with LVNC
Ekizler FA et al *Ann Noninvasive Electrocardiol 2020* [28•]	161	65.8%	42.5 ± 15.2	LVNC	Positive T-wave amplitude in lead aVR (TaVR) in 41%	TaVR associated with higher rates of arrhythmic events, hospitalization for heart failure, and death
Ergul Y et al *Ann Noninvasive Electrocardiol 2011* [17]	23 (plus 50 controls)	17 (74%)	4 years (8 days–16 years)	Isolated LVNC	ECG abnormalities in 87%. The most frequent: LVH (30%), ST-segment depression (43%), and negative T-wave (74%) particularly in the DII, DIII, aVF, and V_4-V_6 leads In 43% QTc longer than the reference value for age	LVH and repolarization abnormalities not unique to the disease but related to the severity of the cardiomyopathy
Gungor B et al *Indian Pacing Electrophysiol J 2013* [23]	1	Female	23	LVNC + other cardiac abnormalities (congenital)	Sinus node dysfunction with symptomatic bradycardia	Sinus node dysfunction
Howard TS et al *J Card Fail 2019* [33]	348	64%	6.8 (0.51–13.75)	LVNC	In 11% (and cardiac dysfunction in 84% of those patients)	WPW common among children with LVNC and associated with cardiac dysfunction
Ning XH et al *Can J Cardiol 2012* [27]	64	49 (77%)	44	LVNC	f-nQRS and f-wQRS present in 38% and 11% of patients respectively	Prognostic value of f-nQRS
Shoji M et al *Circ J 2010* [30]	187	122 (65.2%)	41.3 ± 16.8	LVNC	ECG abnormalities in 73.4%. ST-T changes in 35.2% and bundle branch block in 14.9%. Notably, Brugada-like ECG seen in 3.2%	Most of the ECG abnormalities non-specific. The incidence of these ECG findings not dependent upon the extent of non-compaction

Table 1 (continued)

Study	Sample size	Male gender	Age	LVNC phenotype	Prevalence and type of ECG abnormalities	Key message
Steffel J et al *Am J Cardiol 2009* [22]	78	71%	42 ± 16	LVNC	ECG abnormalities in 87%	No ECG findings or patterns specific for LVNC. Overlap observed between the presence of intraventricular conduction delay (LBBB, in particular), atrial conduction delay, and prolongation of the QTc and reduced systolic LV function, and LV/left atrial dilation
Steffel J et al *Circ J 2011* [74]	74	53 (72)	42.6 (± 16.3)	Isolated LVNC	ECG abnormalities in 86%	PQ duration, QTc duration and repolarization abnormalities in the inferior leads independent predictors of a poor prognosis in LVNC
Stöllberger C et al *Cardiology 2007* [65]	86	65 (75.6%)	52 ± 14	LVNC and NMD	ECG abnormalities in 90%. Tall QRS complexes the most frequent abnormality (43%), followed by ST/T-wave abnormality (37%) and LBBB (20%) The prevalence of ECG abnormalities not different between patients with and without NMD	No ECG pattern typical for LVNC. ECG abnormalities occur independently of presence or absence of NMD
Stöllberger C et al *Int J Cardiol 2009* [75]	102	30 females	53 ± 16	LVNC with and without NMD	AF present in 15 patients (15%)	AF associated with poor prognosis
Stöllberger C et al *Ann Noninvasive Electrocardiol 2013* [19]	141	62.2%	54 ± 1 7	LVNC	ECG abnormalities in 89% PR interval > 200 ms in 16% QRS duration > 120 ms in 19%, a QTc interval > 440 ms in 38%	Prolonged QRS complexes, PR and QTc intervals in LVNC associated with HF and LV dilatation, but not with NMD
Stöllberger C et al *Ann Noninvasive Electrocardiol 2014* [66]	105	69 (66%)	55 ± 17	LVNC and NMD	The most frequent new ECG abnormalities in follow-up ECGs were ST/T-wave abnormalities ($n = 35$), followed by left anterior hemiblock ($n = 6$) and Q waves ($n = 6$)	LVNC patients frequently develop new ECG abnormalities of prognostic relevance. Yearly ECG recommended to look especially for AF, for an increase in the duration of the PQ interval or the QRS width and low voltage ECG

Table 1 (continued)

Study	Sample size	Male gender	Age	LVNC phenotype	Prevalence and type of ECG abnormalities	Key message
Van Malderen S et al *Ann Noninvasive Electrocardiol 2017* [31]	101	44% (in the group with PVCs in all 12 leads)	42.4 (23–80)	LVNC	PVCs in 54%. Ninety-five percent of PVCs did not originate from LV non-compacted myocardial areas	PVCs in LVNC mainly originate from the conduction system and related myocardium
Zhou H et al *Int J Cardiovasc Imaging 2017* [78]	32 and 14 controls	61% in the normal QTc group and 46% in the prolonged QTc group	36.50 ± 15.68 (normal QTc) 49.92 ± 10.77 (prolonged QTc)	LVNC	NA	Prolonged QTc interval associated with more severe compacted myocardial fibrosis, poorer cardiac dysfunction and poorer prognosis in LVNC patients

LVNC left ventricular non-compaction, *ECG* electrocardiographic, *VT/VF* ventricular tachycardia/ventricular fibrillation, *LBBB* left bundle branch block, *ER* early repolarization, *fQRS*. fragmented *QRS*, *TaVR* positive T-wave amplitude in *aVR* lead, *LVH* left ventricular hypertrophy, *WPW* Wolff Parkinson White, *fnQRS/fwQRS* fragmented narrow/wide *QRS*,, *LV* left ventricle, *NMD* neuromuscular disorders, *AF* atrial fibrillation, *HF* heart failure, *PVCs* premature ventricular complexes

arrhythmias and the presence of micro-reentry circuits in the trabeculated myocardium, epicardial coronary hypoperfusion, abnormal ion channel activity and microvascular dysfunction have been hypothesized [20, 31].

Ventricular Pre-excitation

Pre-excitation can be observed in patients with LVNC, especially in children [15]. Wolff-Parkinson-White (WPW) syndrome has been found in 0–3% of adult patients and 8–17% of paediatric patients [13, 15, 16, 18, 20, 32]. In a retrospective study, WPW was found to be an independent risk factor for the development of significant cardiac dysfunction in LVNC [33].

Supraventricular Arrhythmias

Supraventricular arrhythmias, including focal atrial tachycardia, atrial fibrillation (AF) and other paroxysmal supraventricular tachyarrhythmias are commonly observed in LVNC, with variable reported prevalences (18–20,24). The most common supraventricular arrhythmia in adults with LVNC is AF, with a prevalence varying from 0.4 to 39% [14, 16, 19, 20, 34, 35]. Although AF pathogenesis in LVNC is often linked to secondary structural remodelling of both atria, a primary atrial myopathy is another proposed mechanism [36]. The most commonly reported supraventricular arrhythmia in children with LVNC is atrioventricular reentrant tachycardia and focal atrial tachycardia with a prevalence ranging from 6 to 13% [13, 15, 20, 36].

The ECG in Isolated LVNC

Familial occurrence in LVNC ranges from 12 to 50% of cases [37]. Although autosomal dominant or X-linked patterns are most common, autosomal recessive and mitochondrial inheritance, as well as chromosome defects have also been reported. Many of the pathogenic variants found in LVNC are shared with other cardiomyopathies, mainly dilated cardiomyopathy (DCM) and HCM [21]. Pathogenic variants are localised in genes encoding sarcomeric, cytoskeletal or ion channel proteins and those involved in cellular energy metabolism [21, 38]. The ECG patterns in some of the most common LVNC-associated genotypes are reported in Table 3 [38–54].

Left Ventricular Non-compaction in Association With Other Conditions

LVNC may be associated with other cardiac and non-cardiac conditions, including cardiomyopathies, congenital heart diseases and inherited systemic diseases.

Table 2 Main electrocardiographic features in isolated left ventricular non-compaction

ECG feature	Patient no	Male gender	LVEF (%)*	Prevalence of the specific ECG abnormality
Left atrial abnormalities (heterogeneous definition)				
Steffel et al. [22] (P mitrale)	78	71%	40 ± 19	26%
Ergul et al. [17] (atrial dilatation)	23	74%	46% (18–73%)	13%
Chin et al. [13] (broad or peaked P waves)	8	62%	-	37%
Atrial fibrillation				
Oechslin et al. [16]	34	74%	33 ± 13	26%
Sedaghat-Hamedani et al. [34]	68	70%	38 ± 15	29%
Murphy et al. [79]	45	62%	-	7%
Steffel et al. [22]	78	71%	40 ± 19	4%
Salazar-Mendiguchia et al. [35]	75	68%	32 [29–34]	39%
Stöllberger et al. [19]	141	65%	-	17%
Brescia et al. [20]	242	60%	8–51%	0.4%
Pre-excitation				
Pignatelli et al. [18]	36	55%	30% (15–66%)	17%
Brescia et al. [20]	242	60%	8–51%	8%
Ichida et al. [15]	27	56%	61%	15%
Oechslin et al. [16]	34	74%	33 ± 13	0%
First degree atrioventricular (AV)-block				
Steffel et al. [22]	78	71%	40 ± 19	15%
Stöllberger et al. [19]	141	65%	-	17%
Tsai et al. [24]	46	50%	50% ± 18%	11%
Chin et al. [13]	8	62%	-	25%
Left bundle branch block (LBBB)				
Sedaghat-Hamedani et al. [34]	68	70%	38% ± 15	22%
Steffel et al. [22]	78	71%	40 ± 19	19%
Murphy et al. [79]	45	62%	-	29%
Stöllberger et al. [19]	141	65%	-	21%
Oechslin et al. [16]	34	74%	33 ± 13	44%
Ergul et al. [17]	23	74%	46% (18–73%)	0%
Right bundle branch block (RBBB)				
Sedaghat-Hamedani et al. (supplementary data) [34]	68	70%	38% ± 15	3%
Steffel et al. [22]	78	71%	40 ± 19	3%
Stöllberger et al. [19]	141	65%	-	5%
Oechslin et al. [16]	34	74%	33 ± 13	12%
Left ventricular hypertrophy (LVH)				
Steffel et al. [22]	78	71%	40 ± 19	38%
Stöllberger et al. [19]	141	65%	-	30%
Ergul et al. [17]	23	74%	46% (18–73%)	30%
Tsai et al. [24]	46	50%	50% ± 18%	43%
QRS notch				
Steffel et al. [22]	78	71%	40 ± 19	47%
Ning et al. [27]	64	80%	42 ± 14	48%
Cetin et al. [80]	88	65%	32 ± 12	53%
Prolonged QTc				
Brescia et al. [20]	242	60%	8–51%	9%
Stöllberger et al. [19]	141	65%	-	38%
Steffel et al. [22]	78	71%	40 ± 19	52%
Ergul et al. [17]	23	74%	46% (18–73%)	43%

Table 2 (continued)

ECG feature	Patient no	Male gender	LVEF (%)*	Prevalence of the specific ECG abnormality
T-wave inversion				
Pignatelli et al. [18]	36	55%	30% (15–66%)	19%
Brescia et al.[20]	242	60%	8–51%	39%
Steffel et al. [22]	78	71%	40 ± 19	41%
Murphy et al. [79]	45	62%	-	16%
Ergul et al. [17]	23	74%	46% (18–73%)	74%

*LVEF (left ventricular ejection fraction); range is added in brackets when available

Other Cardiomyopathies

LVNC may present as a distinct cardiomyopathy or in association with DCM, HCM and ACM [55, 56]. Clinical studies have investigated the role of imaging techniques in differential diagnosis or in the identification of overlapping phenotypes. In this context the ECG might be useful in the diagnostic process, as it is usually the expression of the predominant phenotypic features [57, 58•].

Congenital Heart Diseases

LVNC may be associated with congenital heart diseases (CHD) [21]. In a large series of 202 adult patients with LVNC, Stähli et al. reported an association with CHD in 12% of cases, including left ventricular outflow tract abnormalities and Ebstein anomaly (EA). In this study, the prevalence of LVNC in patients with EA was 15% [59]. In another retrospective analysis of 84 patients with EA, 4 (5%) had LVNC [60]. In a paediatric cohort of 61 patients with EA, 10 (16%) showed features of LVNC; interestingly, there were no significant differences in the ECG findings; incidence of RBBB, ventricular pre-excitation or supraventricular tachycardias were similar in patients with or without EA [61]. EA and LVNC may share the same genetic background; in a cohort of 141 unrelated probands with EA, pathogenic variants in myosin heavy chain 7 (MYH7) gene (all except for 1 3-bp were missense variants) were found in 8 patients (6 of which had LVNC) [39]. LVNC has been described also in association with tetralogy of Fallot [59]. In a Japanese series of 53 patients with LVNC and CHD, 29 [55%] had ventricular septal defects, 17 [32%] atrial septal defects, 10 patent ductus arteriosus (PDA) and 7 [13%] had EA and double outlet right ventricle); fragmented QRS was observed in 16 patients (40%), followed by RBBB (25%), T-wave abnormality (20%), Q waves (17%), ST-segment depression (12%) and prolonged QT interval (12%) [62].

Neuromuscular Disorders

The combination of an NMD and LVNC may be found in the context of genetic conditions due to pathogenic variants in dystrophin, dystrobrevin, lamin, ZASP (Z-band alternatively spliced PDZ-motif protein) or in the context of metabolic diseases such as infantile glycogenosis type II (Pompe's disease), myoadenylate-deaminase deficiency, or other conditions such as Barth

Table 3 ECG findings in LVNC in specific genetic mutations

Gene involved	ECG findings
MYH7 [47, 48]	AF, first-degree AVB, LVH, LBBB
ACTC1 [49]	RBBB, LAH, RA (T-wave inversion in the anterolateral leads), VEBs
TAZ [50]	RA (ST flattening, T-wave inversion, prolonged QTc)
SCN5A [51, 52]	SSS, AF, pre-excitation, Mobitz-type 2nd degree AVB, complete AVB, RA (prolonged QTc, Brugada pattern), VEBs, VT, VF
LMNA [40, 48, 53, 54]	AF, first-degree AVB, RA, VEBs, VT, VF
RYR2 (41–44)	Polymorphic VT, VF, SSS, VEBs, AV conduction disturbances, AF, RA (ST flattening, T-wave inversion)
HCN4 [45, 46]	Sinus bradycardia
DSP [38]	NSVT, sustained ventricular tachycardia

MYH7 myosin heavy chain 7, *ACTC1* cardiac muscle alpha actin, *TAZ* tafazzin, *SCN5A* sodium voltage-gated channel alpha subunit 5, *LMNA* lamin A/C, *RYR2* cardiac ryanodine receptor type 2, *HCN4* hyperpolarization activated cyclic nucleotide gated potassium channel 4, *DSP* desmoplakin, *AF* atrial fibrillation, *AVB* atrioventricular block, *LAH* left anterior hemiblock, *LBBB* left bundle branch block, *LVH* left ventricular hypertrophy, *NSVT* non-sustained ventricular tachycardia, *RA* repolarization abnormalities, *RBBB* right bundle branch block, *RYR2* cardiac ryanodine receptor type 2, *SSS* sick sinus syndrome, *VEBs* ventricular ectopic beats, *VF* ventricular fibrillation, *VT* ventricular tachycardia

syndrome, Friedreich ataxia or Charcot-Marie-Tooth disease [63]. The ECG abnormalities usually reflect the mixed phenotype.

In a CMR study of patients with Duchenne muscular dystrophy (DMD), LVNC criteria were met by 27/96 patients (28% prevalence) [64]. In another cohort of 86 adult patients with LVNC, 53 (62%) had associated NMDs. A specific NMD was diagnosed in 21 (metabolic myopathy in 14, Leber's hereditary optic neuropathy in 3, myotonic dystrophy in 2, Becker muscular dystrophy in 1 and DMD in 1, respectively). The presence of ECG abnormalities did not differ between patients with or without NMDs. In this study, high QRS voltages, ST/T wave abnormality and LBBB were the most frequently observed ECG abnormalities [65, 66].

Metabolic Conditions

LVNC has been described in association with monogenic syndromes, including metabolic conditions (e.g. storage diseases such as Danon disease) [55]. The hypothesised mechanism responsible for the development of increased trabeculations in storage disorders might be represented by abnormal intramyocardial storage; whether an immunologic reaction to abnormal proteins or storage material triggers the development of increased trabeculations remains speculative [67]. Danon disease is a rare, X-linked dominant disorder characterised by left ventricular hypertrophy, cardiac conduction abnormalities, skeletal muscle weakness and mild intellectual disability, and is caused by variants in the LAMP2 gene [68]. An association between Danon disease and LVNC has been reported [55]. ECG signs of pre-excitation are common and present in up to 70% of affected male patients [68].

Barth Syndrome

Barth syndrome (BTHS) is a rare X-linked genetic disease characterised by cardiomyopathy (most commonly LVNC), skeletal myopathy, neutropenia and organic aciduria [69, 70]. The main gene involved in BTHS is tafazzin (TAZ) located at Xq28 which encodes an acyltransferase that catalyses the remodelling of cardiolipin in mitocondrial membranes [69]. Several pathogenic variants in the tafazzin gene have been described. Spencer et al. reported prolonged or borderline prolonged QTc in a high proportion of BTHS patients (43%), although this feature did not appear to correlate with episodes of documented ventricular arrhythmias [71].

Differential Diagnosis With Cardiac Adaptation to Exercise

Highly trained athletes may show some degree of LV trabeculations. In a large study of over 1000 asymptomatic athletes, 8.1% fulfilled conventional echocardiographic criteria for LVNC [5]. Increased LV trabeculations were more common in athletes of African/Afro-Caribbean origin. As the majority of athletes with excessive trabeculation did not exhibit any other cardiomyopathic features, it has been postulated that this may be an exercise-induced remodelling phenomenon [72]. Increased cardiac preload is the most probable mechanism for increased trabeculation in the majority of athletes [8]. Differential diagnosis is extremely relevant, but at the same time challenging. The ECG may help in this setting, keeping in mind that the athlete's heart ECG is also often abnormal [7]. Significant differences in the pattern of T-wave inversion may help in discriminating between physiological cardiac remodelling and LVNC (Fig. 2). Patients with LVNC often show T-wave inversion in the inferolateral leads, whereas athletes either show a normal ECG or T-wave inversion in V1–V3, a pattern that has been recognised as physiological especially in black athletes and if accompanied by J point elevation [73].

ECG in the Management and Risk Stratification of Patients With LVNC

ECG abnormalities carry a prognostic role in patients with LVNC. Although a normal ECG is uncommon in LVNC, patients with a normal ECG have a lower degree of structural and functional echocardiographic abnormalities and appear to have a better prognosis [16, 17, 19, 22, 74]. On the contrary, some ECG findings suggest a malignant phenotype and might influence the surveillance of patients at higher risk of adverse events [16, 20, 36]. For example, atrial fibrillation (both permanent and paroxysmal) has been associated with a more severe clinical picture of heart failure and higher mortality in several studies [16, 19, 36, 66, 75, 76]. The association between LVNC and a pre-excitation pattern consistent with WPW syndrome is associated with a greater risk of development of a dilated phenotype and systolic dysfunction [33].

Intraventricular conduction delay (mainly LBBB) in LVNC, as well as in other cardiomyopathies, is associated with reduced LV systolic function, heart failure and LV dilation [19, 74]; further studies are required to better define the prognostic role of this ECG abnormality. As in other cardiac conditions characterised by severe LV systolic dysfunction, the presence of LBBB may be an indication for the use of cardiac resynchronization therapy (CRT) [77]. Although some ECG abnormalities (e.g. positive TaVR) represent ominous signs significantly and independently associated with lethal arrhythmic events including sudden death, their presence does not represent per se an indication for an implantable cardioverter-defibrillator (ICD) [28•]. The decision on whether or not to implant an ICD for primary prevention of sudden cardiac death should be balanced,

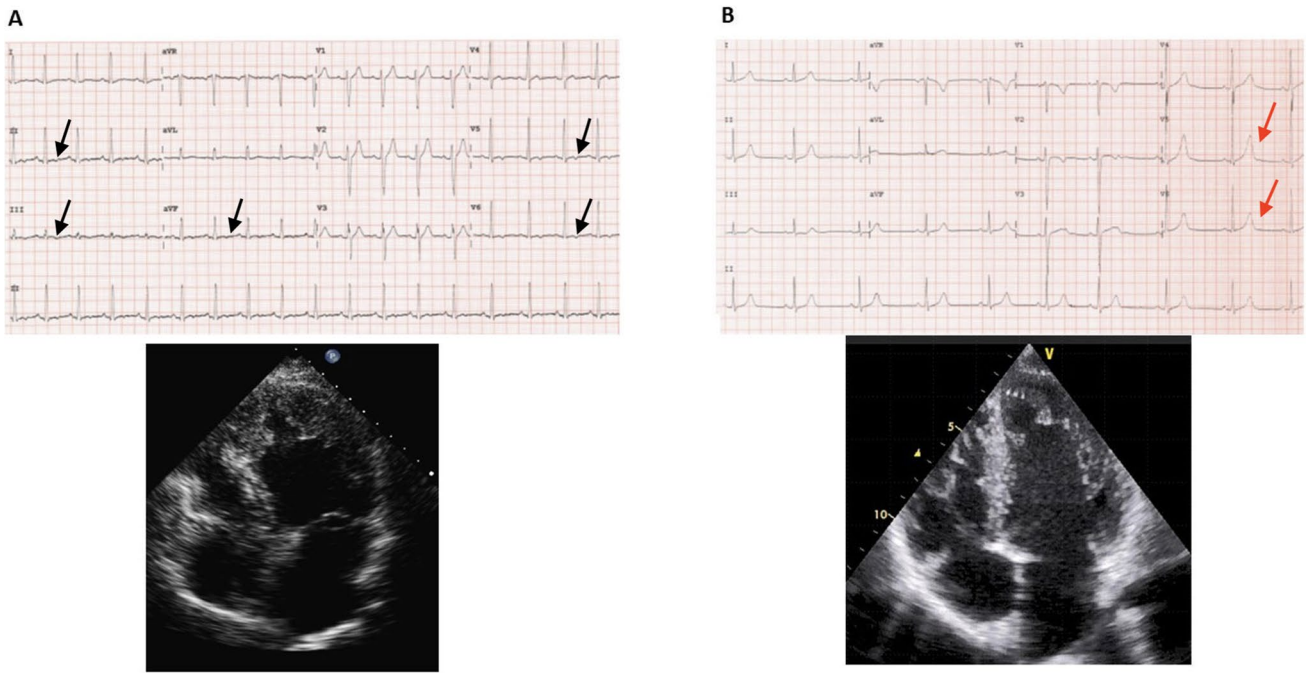

Fig. 2 Twelve-lead electrocardiogram in two cases of augmented left ventricular trabeculation (echocardiographic apical 4-chamber view). Thirty-year-old male with familial LVNC. Black arrows indicate non-specific repolarization abnormalities in limb leads, Goldberger's leads and lateral precordial leads (**a**). Twenty-two-year-old cyclist with increased left ventricular trabeculation. ECG is normal with high, but physiological T-waves (red arrows) (**b**)

taking into account both family and patients' clinical history, symptoms and instrumental features (ECG, ambulatory ECG monitoring, echocardiography, CMR). High QRS voltages have been associated with higher mortality and systemic embolism (probably due to profound alterations of myocardial structure that can predispose to the development of intraventricular thrombi) [22, 66]. Stöllberger et al. studied 105 patients with LVNC over a mean follow-up of 3.6 years, and they compared the ECG features of surviving and deceased patients; multivariate analysis identified atrial fibrillation, low voltages, increase in QRS width and high QRS voltages as predictors of poor outcome [66]. Repolarization abnormalities seem to be linked to increased mortality in some studies [20, 74]. In a cohort of LVNC patients with an average follow-up of 57 months (0–153.4 months), repolarization abnormalities (ST-segment depression or elevation > 0.1 mV in limb leads and > 0.2 mV in precordial leads or T-wave inversion) in the inferior leads were independently associated with poor outcome, with an increased risk for cardiovascular death or heart transplantation [74]. The presence of a prolonged QT interval has been variably linked with systolic dysfunction, myocardial fibrosis and a higher risk of cardiovascular death [22, 74, 78]. In a subgroup analysis by Steffel et al., the LV ejection fraction in patients with prolonged QT was lower than in patients with QT in the normal range (EF 32.2 ± 15.8% vs 48.5 ± 18, $p < 0.0001$) [26]. Similarly, Zhou et al. found that a prolonged QT was associated with lower LV ejection fraction and higher risk of adverse events [78]. Ventricular arrhythmias are commonly described in patients with LVNC (up to 47%) and are an independent risk factor for mortality [13, 14, 20]. Periodic clinical monitoring with ECG and ambulatory ECG monitoring aimed at detecting ventricular arrhythmias are recommended [20, 25, 36].

Clinical Implications

Several uncertainties about nomenclature and definition of LVNC continue to exist and while the focus and dilemmas concern mainly the imaging assessment of this condition, the ECG provides useful hints that, when appropriately interpreted in the clinical context, might or might not reinforce the diagnostic hypothesis of LVNC. Unfortunately, the lack of specificity of the ECG abnormalities in patients with LVNC described so far, does not allow (if considered in isolation) diagnosis of the condition. Unlike other cardiomyopathies (mainly DCM and HCM), in which some ECG abnormalities may constitute real *red flags* able to guide clinicians towards a specific aetiology, this is currently not the case in LVNC. The main reason, apart from the lack of pathognomonic ECG signs, is that when approaching patients with prominent trabeculations, clinicians are facing diagnostic queries at two different levels: (1) is the observed cardiac

phenotype pathological or not?; (2) what is the specific aetiology? Although we should recognise that grey zones and wide areas of overlap between normal and pathologic phenotypes exist also in the context of other cardiomyopathies (e.g. differential diagnosis between HCM and athlete's heart), the knowledge gaps in the setting of LVNC seem wider. So, does the ECG modify our diagnostic workup in patients with excessive trabeculations, and possibly our management of the underlying condition? Of course, the ECG in isolation is not able to solve the diagnostic conundrum of LVNC; however, when considered in a set of diagnostic criteria including family history, clinical information and imaging features (as already done for ACM), the ECG may differentiate between physiological and pathological findings or may provide clues raising the possibility of specific underlying genetic conditions (Fig. 3). Moreover, some ECG features in patients with LVNC constitute ominous signs that require a stricter patient surveillance or the need of specific therapeutic measures (e.g. ICD implantation).

Gaps in Evidence and Future Suggestions

LVNC diagnostic criteria are traditionally focused on cardiac imaging (echocardiography and CMR). Our knowledge on ECG abnormalities in LVNC mainly derives from single-centre studies, case reports or small case series. The many uncertainties surrounding the definition of LVNC make this entity difficult to grasp, and future studies should include ECG data systematically, in order to identify possible additional roles of the ECG in the diagnosis, risk stratification and clinical management of the disease. The first step should consist of the identification of the ECG abnormalities with higher sensitivity and specificity observed in patients with isolated LVNC cardiomyopathy (clearly differentiating the paediatric population from adults). The second step should be the incorporation of these ECG abnormalities into the diagnostic criteria of the disease. A scoring system (points-based or with major and minor criteria) should be advisable to exit from a diagnostic quagmire.

Conclusions

The ECG remains a cornerstone in the diagnosis and management of patients with cardiomyopathies, including LVNC. Although recent advances in cardiac imaging resulted in enormous progress in the diagnosis and management of LVNC, an approach that is entirely based on phenotypic visualization may lead to erroneous interpretations. An integrated approach including clinical, ECG, imaging data and possibly genetic information in selected cases probably constitutes the best diagnostic approach to this intriguing condition.

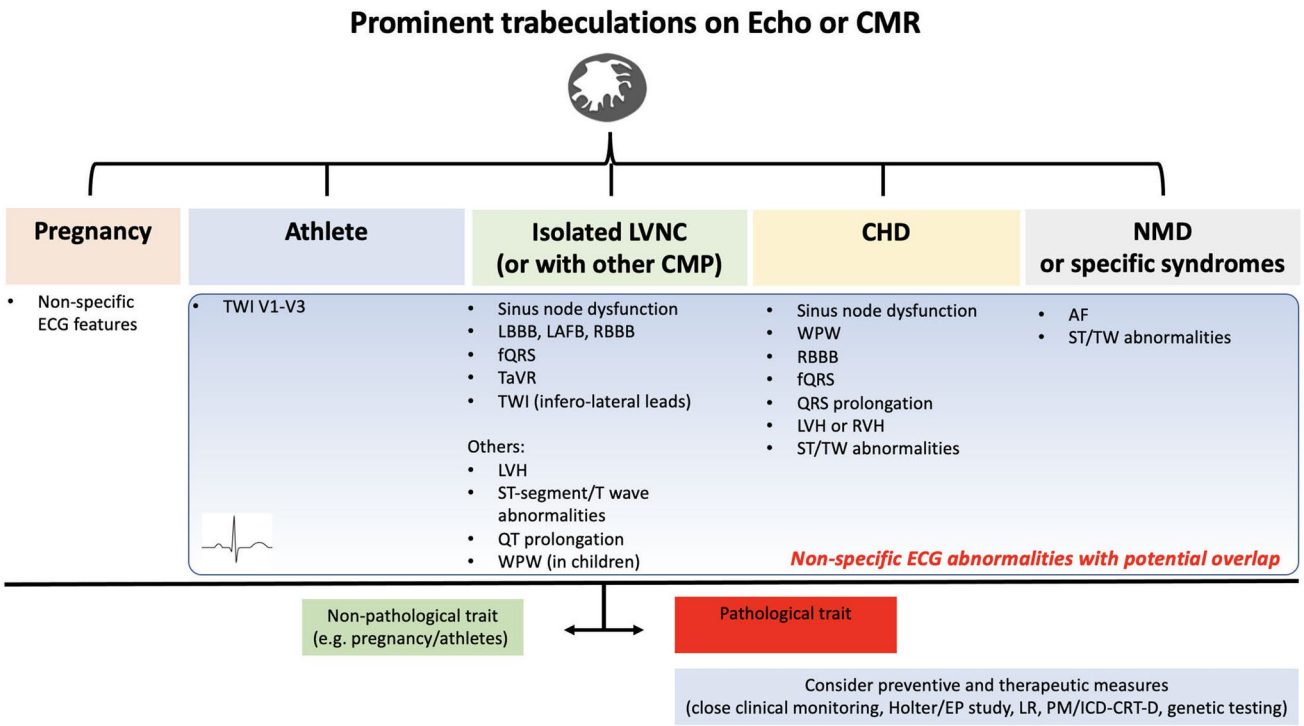

Fig. 3 Contribution of the ECG in the diagnostic workup of patients with hypertrabeculation in different physiological or disease states

Author Contribution Main contributions: GDS, AP, SG, GF (conceptualization); AP, GDS, GF (literature search and data analysis); GDS, AP, GP, GS, MP, AP, SS (manuscript drafting); SG and GF (manuscript critical revision as senior authors). All the authors were actively involved in all the stages of the project.

Availability of Data and Material Not applicable for this type of manuscript.

Code Availability Not applicable.

Declarations

Ethics Approval Not applicable (not required for this type of article).

Consent to Participate/Consent for Publication Not applicable for this type of manuscript.

Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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