Predictors of poor outcome in patients with left ventricular noncompaction: Review of the literature

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Abstract

Left ventricular noncompaction (LVNC) is a unique inherited cardiomyopathy, characterized by an increased risk of adverse cardiovascular events such as heart failure, arrhythmia or sudden cardiac death. Although in comparison to dilated cardiomyopathy, the number of clinical studies concerning LVNC is still small, it is quickly increasing, which reflects a huge effort of the cardiovascular society to develop data to improve understanding of this cardiomyopathy. However, the predictors of adverse outcomes in LVNC are not well established. The aim of this review is to systematize the available data obtained from the medical literature in order to establish a proper prognosis, so that affected patients can receive the most appropriate treatment. The review considers issues connected with various areas of risk in LVNC, referring to its incidence and prevalence, comorbidity, genetics, morphology, symptoms, thromboembolic events, incidence of arrhythmia, sudden cardiac death, and mortality. Beginning with a genetic approach to the disease, passing through diagnostic tools, and finishing with issues relating to invasive methods of treatment, the article points out the most important and valuable clues for predicting a poor prognosis in LVNC. The review confirms that LVNC is not a disease, but a type of cardiac abnormality laden with a variety of prognostic factors of poor outcomes in terms of life-threatening ventricular arrhythmia and progression of heart failure. Thus, establishing a proper prognosis for individual patients is crucial for implementing the most appropriate treatment, and it should be based on the outcomes of a variety of clinical tests.

Key words: cardiovascular risk factors, sudden cardiac death, left ventricular noncompaction

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Left ventricular noncompaction (LVNC) is a unique inherited cardiomyopathy that has gained increasing attention in the past decade.[1] It was first described in 1926 by R.T. Grant and it is characterized by a spongy morphological appearance of the left ventricular (LV) myocardium due to prominent trabeculae and deep intertrabecular recesses.[1–3] Left ventricular systolic dysfunction, heart failure, thromboembolism, arrhythmia, and sudden cardiac death (SCD) occur in the natural history of this cardiomyopathy, which is characterized by an increased risk of adverse cardiovascular events.[3] Despite the increasing efforts of the cardiovascular community to better understand LVNC, clinical research remains limited and the predictors of adverse outcomes of LVNC are not well-established.

The aim of this review is to summarize contemporary (2000 to 2015) literature about LVNC regarding its incidence and prevalence, comorbidity, genetics, morphology (and morphological mimicry), symptoms, thromboembolic events, incidence of arrhythmia, SCD, and mortality. Special attention was paid to predictors of adverse outcomes in patients with LVNC.

Prevalence

Left ventricular noncompaction is diagnosed in 0.05% to 0.26% of adult patients referred for echocardiographic examinations, with male predominance; however, some studies report a prevalence from 0.01% to 1.3% in the general population.[1,4,5] In the affected patients, LVNC is the cause of heart failure in 3–4/100 individuals.[5] The rate of familial involvement appears to vary from 18 to 33%.[4]

Genetics

The genes involved in this cardiomyopathy generally encode sarcomeric or cytoskeletal proteins. In cases of LVNC with congenital heart disease, disturbances of the NOTCH signaling pathway may occur, and the genetic basis of LVNC may play an important role in estimating the risk of adverse outcomes. It is known that LVNC may have incidental as well as familial origins. The literature provides some information on associations of LVNC with a number of mutations in the genes that are probably responsible for its occurrence, for the higher risk of adverse outcomes and for the familial incidence (Table 1).[5–7] Klaassen et al. noticed that sarcomeric gene mutations account for approx. 17% of LVNC cases.[8] In other studies, associations of LVNC with a wide number of genetically determined syndromes and the molecular background of these mutations have been reported (Table 2, 3).[9–11]

From the clinical point of view, it is worth pointing out some aspects of the genetically-induced poor outcomes in LVNC. Xu et al. noticed that some gene mutations are similar in various types of cardiomyopathies, e.g.,

Table 1. Proteins with possible genetic modifications in reference to left ventricular noncompaction (LVNC)

Proteins with gene mutations probably responsible for the occurrence of LVNC
1. tafazzin (G4.5, TAZ) 2. dystrobrevin (DTNA) 3. lamin A/C (LMNA) 4. mitochondrial proteins 5. frataxin 6. tropomyosin 1 (TPM 1) 7. alpha-actin (ACTC) 8. protein SCN5A 9. myosin binding protein C (MYBPC3) 10. cardiac troponin T (TNNT2) 11. cardiac troponin I (TNNI3) 12. beta-myosin heavy chain (MYH7) 13. other
Proteins with gene mutations associated with worse outcomes in LVNC (heart failure, conduction disturbances, ventricular arrhythmia and sudden cardiac death)
1. protein SCN5A 2. myosin binding protein C (MYBPC3) 3. cardiac troponin T (TNNT2) 4. cardiac troponin I (TNNI3) 5. beta-myosin heavy chain (MYH7)
Genes responsible for familial incidence of LVNC
1. *G4.5* gene (TAZ) mutations

Table 2. Genetically determined syndromes associated with left ventricular noncompaction

1. dystrophinopathies	16. neuromuscular disorder
2. dystrobrevinopathies	17. Nail-patella syndrome
3. myotonic dystrophy type 1 and 2	18. Melnick-Needles syndrome
4. zaspopathy	19. MIDAS syndrome
5. myoadenylate-deaminase deficiency	20. DiGeorge syndrome
6. Charcot-Marie-Tooth disease	21. Beals-Hecht syndrome
7. mitochondrial disorder	22. congenital adrenal hyperplasia
8. Barth syndrome	23. distal 4q trisomy/distal 1q monosomy
9. laminopathy	24. del 1q syndrome
10. Friedreich ataxia	25. distal 5q deletion
11. Pompe's disease	26. monosomy 1p36
12. Turner syndrome	27. trisomy 11
13. Ohtahara syndrome	28. trisomy 13
14. Roifman syndrome	29. LEOPARD syndrome
15. Noonan syndrome	

Table 3. Genetically determined syndromes associated with a higher incidence of left ventricular noncompaction (LVNC) in relation to the type of molecular disorder

1. Mutations within the same group of genes associated with LVNC: a) associated with cardiac-specific loss of succinate dehydrogenase b) mutations in TTR gene – DiGeorges syndrome c) mutation in TAZ gene – Barth syndrome
2. Mutations directly linked to the contractile apparatus: a) mutations in MYH8 gene – Beals-Hecht syndrome b) mutations in FLNA gene – Melanick-Needles Syndrome
3. Mutations connected with poor prognosis and indirectly connected with LVNC: a) potassium channel, voltage gated KQT-like subfamily Q, member 1 – *KCNQ1* – congenital adrenal hyperplasia

TTR – transthyretin; TAZ – taffazine; MYH8 – myosin heavy chain 8; FLNA – filamin A.

mutations in the beta-myosin heavy chain (βMHC) and cardiac troponin T (cTnT) genes.[12] These mutations are associated with hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), restrictive cardiomyopathy (RCM) as well as LVNC. The authors also noticed that some mutations are responsible for changing the phenotype from HCM to LVNC and from DCM to LVNC. In addition, some mutations can be classified as benign/mild (with low to moderate penetrance, causing only mild symptoms of heart failure with no incidence of SCD or necessity for heart transplantation), and some as moderate/malignant (with high penetrance, early-onset age, moderate to severe symptoms, heart failure in NYHA functional class III–IV and SCD), i.e., the malignant *cTnT Arg131Trp* mutation associated with both DCM and LVNC.[12] Xu et al. suggested a possible connection between the mechanisms of decreasing Ca^{2+}-sensitivity in mutations associated with LVNC and DCM. They also considered a possible similarity in genetic mechanisms in patients who progressed from HCM to DCM and in those who progressed from HCM to LVNC, which might suggest phenotypical continuity between cardiomyopathies or an "overlap cardiomyopathy syndrome". This hypothesis was supported by a more recent demonstration of cTnT mutations in RCM and LVNC patients, which may lead to difficulty in clinically diagnosing these phenotypes.[12]

The genetic basis may also be responsible for poorer outcomes in patients with LVNC and atrioventricular or intraventricular conduction disturbances (i.e., left bundle branch block) or ventricular arrhythmia. The key examples are mutations in the *SCN5A* gene (responsible for isolated cardiac conduction defects and associated with an increased susceptibility for lethal ventricular arrhythmia), which are seen not only in LVNC but also in Lev's disease and in the LQT3 syndrome. The increased cardiovascular risk of ventricular arrhythmia in LVNC is also noticed in other gene mutations, i.e., beta-myosin heavy chain gene (*MYH7*) mutations. This mutation also tends to occur in Brugada syndrome and severe form of HCM (early onset, complete penetrance, and increased risk of SCD). In addition, the pathogenesis of HCM is associated with mutations of the gene encoding for troponin T and I, and also for MYBPC3. Mutations in the latter gene are responsible for the inability of the cardiac myosin-binding protein C to interact with myosin and titin. All these gene mutations may also occur in LVNC and may be responsible for increasing cardiovascular risk of the disease.

In conclusion, ion channel and contractile protein gene mutations influence the clinical presentation of LVNC and its outcome. The genetic basis and similarities to other cardiac and muscle diseases make LVNC something more than a cardiac disease: it is a systemic muscle disease dependent on the severity of gene penetration in other neuronal and muscular tissues.

It has been reported in different studies that the prognosis of LVNC also depends on cardiac and neuromuscular comorbidity.[10] Furthermore, the genetic similarity to DCM and HCM may induce not only a genetic but also an anatomical overlap syndrome, which may hinder the diagnosis of LVNC in echocardiographic examination.

Right ventricular involvement

Concomitant damage of the right ventricle (RV) in LVNC is not rare and it can be difficult to distinguish between noncompaction and arrhythmogenic right ventricular cardiomyopathy (ARVD). Although the criteria for ARVD were established in 1994 by the ARVD Task Force, the presence of RV enlargement, abnormal global RV wall motion, focal hypokinesis or dyskinesis, bulges concomitant with a two-layer RV structure, a prominent endocardium and excessive trabeculation – even if they coexist with typical LV morphology for LVNC – may lead to a diagnosis of ARVD rather than LVNC. Włodarska et al. examined 9 individuals (7 males), mean age 37.9 years, with a negative family history and initial diagnosis of ARVD, who presented with palpitations, syncope, pre-syncope and fatigue. Sustained (VT) or non-sustained ventricular tachycardia (nsVT) of LV-origin morphology was recorded in 3 out of the 9 patients and polymorphic VT in 2 of them. Endomyocardial biopsies were performed, and the diagnosis of ARVD was confirmed in only 1 individual, showing a damaged myocardium surrounded by fibro-fatty tissue, which is distinctive for ARVD.[13]

The involvement of the RV in the pathologic process of LVNC is essential in patients referred for cardioverter-defibrillator (ICD) implantation. Sakai et al. indicated that due to a thinner RV wall, its involvement in LVNC pathology makes it prone to perforation in the presence of an ICD lead.[14]

Left ventricular noncompaction in children

Left ventricular noncompaction is the third most common cardiomyopathy in the pediatric population, after dilated and hypertrophic cardiomyopathies.[1] Children affected by LVNC have a lower general incidence of heart failure than adults; however, mortality in symptomatic LVNC patients is higher in children and adolescents (9–10% per year) than in adults (1–5% per year).[4] The prevalence of ventricular arrhythmias is similar in children and in adults.[15] It is noteworthy that a higher incidence of familial cases is observed in the pediatric population than in adults: approx. 44%. Ozgur et al. reported almost 90% of LVNC children showing ventricular systolic dysfunction and 21% died during the mean observation period (1.3 years ±1.1 years). Tachypnea, a failure to thrive, recurrent pneumonia and fatigue were the most frequent clinical symptoms. An early age at presentation and increased LV end-diastolic diameter were markers of a poor prognosis.[16]

Pregnancy

The prognosis in pregnant women with LV hypertrabeculation/LVNC is uncertain and data is inconsistent. There are also studies that point to LVNC as the cause of peripartum cardiomyopathy.[7] Sarmaa et al. analyzed 12 pregnancies in 7 females with LVNC. Four out of 12 pregnancies were delivered by caesarean sections, 3 by emergency caesarean sections due to fetal clinical condition, and 5 by natural birth. Only 2 out of 7 women developed VT during the postpartum period, but symptoms of heart failure were present in 6 out of 12 pregnancies. Two of the children were diagnosed with LVNC; and 2 out of the 12 newborns died. Finally, the authors reported that 50% of LVNC females developed heart failure symptoms during pregnancy. Ventricular arrhythmias were present in 16% of the pregnancies, and were ultimately treated with ablation or ICD implantation.[4] Stöllberger et al. reported that women with LV hypertrabeculation/LVNC and no evidence of systolic dysfunction or arrhythmias can proceed through pregnancy without problems.[17] This was in agreement with results reported by Gati et al., who performed echocardiography on 102 asymptomatic pregnant women in the first and third trimesters and in the postpartum period. Twenty-six of these women (25%) developed increased trabeculations during pregnancy, and 8 of them fulfilled the criteria for LVNC. During the mean 24-month postpartum observation period, complete resolution was observed in 19 women (73%), and marked reduction in the trabeculated layer in 5 of them. This study shows that pregnancy may induce LV hypertrabeculation in a significant proportion of pregnant women, probably due to increased LV loading conditions.[18] Thus, in pregnant women with LV hypertrabeculation that fulfills the LVNC criteria (especially in those without heart failure symptoms or ventricular arrhythmias) it is very important to determine the final diagnosis after the postpartum period.

Electrocardiography

It has been shown that a standard 12-lead ECG examination can provide information on the risk of adverse outcomes in patients with LVNC. Fragmented narrow or wide QRS complexes are associated with higher mortality and lower left ventricular ejection fraction (LVEF). Moreover, the presence of fragmented narrow QRS complexes seems to be an independent predictor of all-cause mortality and heart transplantation in patients with LVNC.[19] Left bundle branch block (LBBB, 21–44%), atrial fibrillation (7–26%) and VT (4–30%) frequently occur in LVNC, and often are associated with the genetic disorders described above. The overall prevalence of ventricular arrhythmia in LVNC is estimated to be from 6 to 60%, whereas the incidence of SCD is 18%.[4,13] Akhbour et al. reported that LBBB was associated with LV lateral wall involvement. Despite its statistical independence of LVEF, LBBB seemed to be more frequent in patients with LVEF <35%.[20] Akhbour et al. also pointed out that although ECGs are rarely normal in patients with LVNC, risk stratification requires more than a simple ECG strip; a 24-h ECG recording, a 7-day telemetric ECG monitoring/recording or an arrhythmia loop recorder may be helpful in further risk stratification.[21–24]

Cardiac magnetic resonance

A few studies aimed to assess the prognostic role of cardiac magnetic resonance (CMR) imaging in patients with LVNC. In a recent study by Wan et al., late gadolinium enhancement (LGE) in CMR was found in only 19 out of 47 patients diagnosed with LVNC. However, the presence of LGE was associated with a higher incidence of premature ventricular contractions (79% vs 29%; $p < 0.001$) and non-sustained VT (47% vs 7%; $p < 0.003$).[25]

Symptoms

Greutmann et al. diagnosed 132 patients with isolated LVNC in a single-center study and concluded that mortality is especially high in symptomatic patients, and that they are at risk of major adverse events such as systemic embolism, sustained ventricular arrhythmia, and admission to a hospital for heart failure. The predictors of adverse outcomes defined as cardiovascular death and heart transplantation are NYHA functional class III/IV or admission to a hospital due to heart failure symptoms, sustained ventricular arrhythmia, and systemic embolization.[26]

Stöllberger et al. examined 59 inpatients and 54 outpatients with LVNC and noticed that the inpatients were more symptomatic (symptoms of heart failure, exertional dyspnea, palpitations, vertigo, syncope), had higher mortality and a shorter time between LVNC diagnosis and death than outpatients. It is noteworthy that 55% of LVNC patients had heart failure symptoms and 69% had exertional dyspnea. The inpatients were older, more frequently had advanced heart failure, systolic dysfunction, diabetes, and more extensive hypertrabeculation than the outpatients.[27]

Thromboembolism

Thromboembolism is another complication that may be related to LVNC. Thromboembolic events are reported in 5–38% of cases.[4] Stöllberger et al. retrospectively investigated the records of 144 LVNC patients to assess the rate and risk factors of stroke and embolism.[28] Out of 144 subjects, 22 (15%) had undergone a thromboembolic event (stroke in 21 patients and peripheral embolism in one). The cause of stroke or embolism was cardioembolic in

14 cases (64%), atherosclerotic in 5 (23%) and undetermined in 3 (14%). Among the patients with a cardioembolic cause, almost 93% had either atrial fibrillation or LV systolic dysfunction determined as the presence of fractional shortening less than 25%, and almost 29% had both atrial fibrillation and LV dysfunction. The researchers also noted that the prevalence of arterial hypertension and the mean age in patients with stroke or an embolic episode was higher than in those without thromboembolic events (59 vs 32% and 60 vs 53 years, respectively). It should be emphasized that among these 22 individuals, only one patient was on appropriate anticoagulation therapy with low-molecular-weight heparin; the others were treated with 100 mg of aspirin daily or with a vitamin K antagonist with an INR (International Normalized Ratio) below the therapeutic level.[28]

Arrhythmia

The risk of developing severe ventricular arrhythmias such as VT or VF is increased in individuals with LVNC, especially those with LV systolic function impairment. Ventricular tachycardia was present in 36% of adult LVNC patients in a study by Aras et al.[29] In a retrospective study by Kobza et al., 8 out of 12 adult patients (67%) with LVNC had ICDs implanted due to VT; in another report, arrhythmia-induced syncope occurred in 2 out of 18 LVNC patients (10%).[30,31] There is data on the occurrence of polymorphic VT resistant to beta-blockers and requiring ICD implantation.[22] Okubo et al. also observed an increased risk of ventricular arrhythmia (up to 47% of individuals with LVNC), including VT and VF in patients with LVNC and decreased LV systolic function. Those authors suggested that ventricular arrhythmias may account for half of the deaths in LVNC patients.[32] It has also been noted that palpitations in LVNC may suggest self-limiting VT and may be associated with worse outcomes.[21]

Devices and pharmacological therapy

According to some studies, the implantation of ICD devices is recommended in patients with LVNC and ventricular arrhythmia, especially in those with depressed systolic function determined by LVEF less than 31%. The cut-off point of 31% predicts the majority of adverse events (death, heart failure, ventricular arrhythmia, and stroke) in LVNC patients with a sensitivity of 71% and specificity of 90%. However, this particular finding does not conflict with the fact that higher LVEF values (35%) are commonly considered predictive of VT. Published in 2015 (by the European Society of Echocardiography) guidelines on ventricular arrhythmia and SCD stated for the first time that it is reasonable to apply the same therapeutic criteria to LVNC and non-ischemic dilated cardiomyopathy, because of their similarity (Fig. 1). The guidelines state that it is important to take under consideration LV function and the severity of ventricular arrhythmia.[33] However, it should be emphasized that there is no sufficient evidence for ICD implantation in primary prevention in patients with LVNC only due to the presence of LVNC, especially since inappropriate ICD discharges are another risk factor of poor outcome.[34] Kobza et al. reported appropriate ICD discharge in 37% of 30 LVNC patients (42% implanted for secondary and 33% for primary prevention) during 40 months of follow-up.[35] This rate was higher than in the study of Stöllberger et al. where the rate of appropriate discharge was in 3 out of 154 observed patients (2%).[34] This was explained by the difference between groups in the number of implantad CRTs with defibrillators (CRT-Ds), which significantly improved LV systolic function, in 20% vs 67% of the participants, respectively.[34] Furthermore, some authors suggest that, in case of ventricular arrhythmia in patients with LVNC but without severe systolic dysfunction, ICD implantation prevents SCD.[32,36] Okubo et al. suggest that if severe systolic dysfunction and other classical indications for CRT are present, resynchronization therapy should be implemented to cause reverse LV remodeling, resulting in a decrease in the occurrence of fatal ventricular arrhythmia and SCD. It is worth noticing that those authors implanted CRT on the basis of the presence of dyssynchrony in echocardiography.[32] In another report by Stöllberger et al., LV hypertabeculation regressed with LV systolic function improvement, which was seen after the initiation of biventricular pacing.[36]

It has been reported that not only treatment with CRT-Ds but also pharmacological therapy may improve LV function, increase LVEF, decrease the probability of ventricular arrhythmia, and decrease the degree of noncompaction.[4] In fact, worse outcomes are observed when no pharmacological or device therapy is administered, or when the medications or devices used are inappropriate.

Prognosis

There are only a few reports referring to annual mortality from LVNC. Stöllberger et al. consider the prognosis in LVNC at least controversial. In their study, the annual mortality was estimated at 4.81% during 65 months observing 154 patients with LVNC. SCD was observed in 3 patients (2%) during this period, and mortality due to progression of heart failure in 11 patients (7%).[32] In another study of 381 LVNC patients, the 5-year event-free survival rate after diagnosis was estimated at 58%.[8]

Stöllberger et al. noticed a correlation between LVNC and neuromuscular disease, which was associated with a higher risk of arrhythmia.[32] In another study, the same authors reported that inpatients with LVNC and neuromuscular disorders have worse prognoses than outpatients with regard

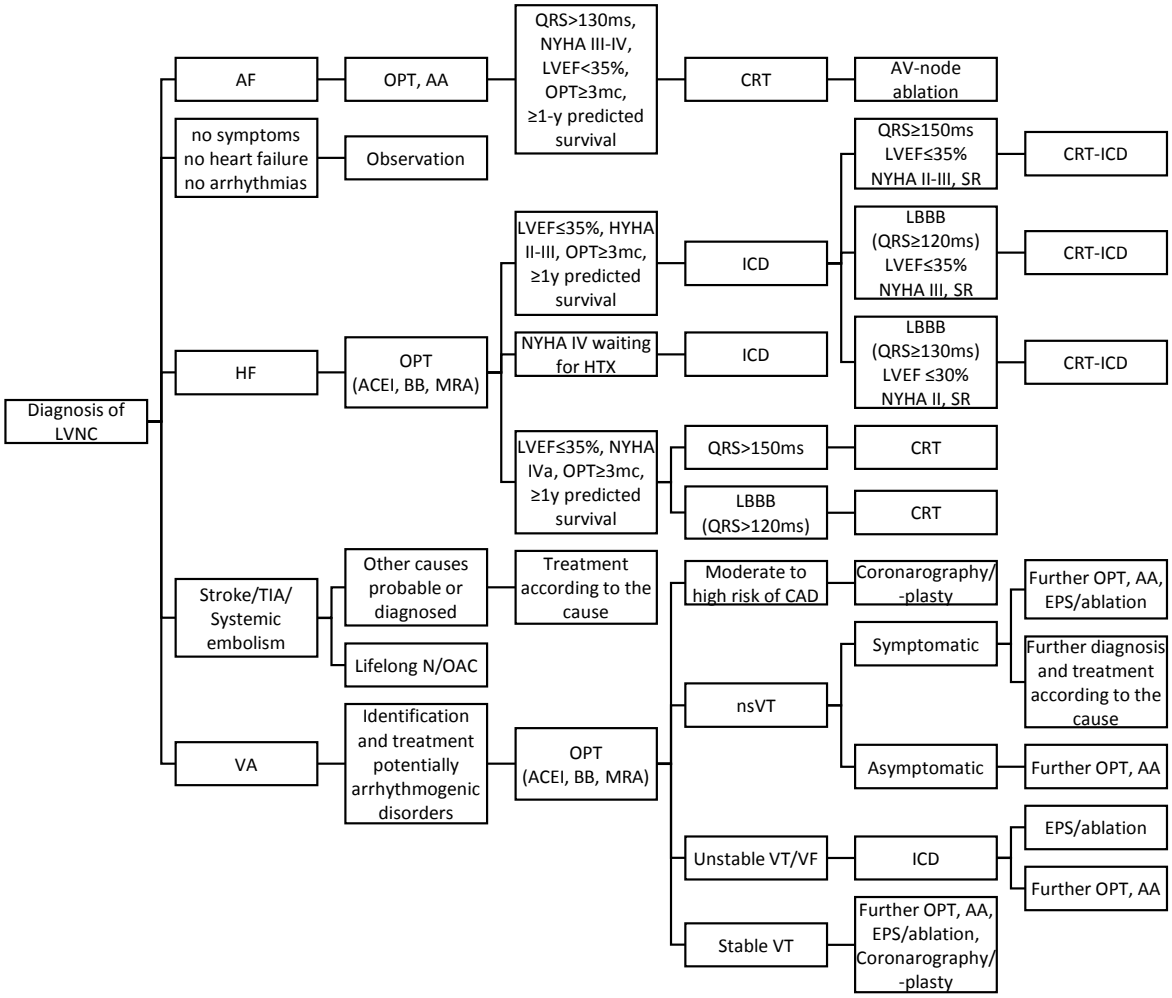

Fig. 1. Therapeutic proceeding depending on the various clinical manifestations of left ventricular noncompaction (LVNC); based on the European Society of Cardiology guidelines for the management of patients with ventricular arrhythmias and prevention of sudden cardiac death (published in 2015)

OPT – optimal pharmacotherapy; AA – anti-arrhythmics; ACEI – angiotensin converting enzyme inhibitor; BB – beta-blockers; MRA – mineralocorticoid receptor antagonists; N/OAC – non-vitamin K antagonist/oral anticoagulants; SR – sinus rhythm; AF – atrial fibrillation; VA – ventricular arrhythmia; VT – ventricular tachycardia; nsVT – nonsustained VT; VF – ventricular fibrillation; ICD – implantable cardioverter-defibrillator; CRT – cardiac resynchronization therapy; CRT-ICD – CRT with ICD; EPS – electrophysiological study; CAD – coronary artery disease; TIA – transient ischemic attack; HF – heart failure; LVEF – left ventricular ejection fraction; NYHA – New York Heart Association scale; LBBB – left bundle branch block; AV – atrioventricular; HTX – heart transplantation.

to neurologic findings and mortality.[27] During a mean follow-up of 3.8 years, the mortality rate was at the level of 5.8% per year. Patients diagnosed with LVNC as inpatients had a significantly higher mortality rate than those diagnosed as outpatients (12.1% vs 2.1% per year, respectively) and a shorter time between LVNC diagnosis and death (1.7 years vs 4.6 years, respectively). The overall mortality during the follow-up was 21.6% due to heart failure (32% of the causes), SCD (13.6%), pulmonary embolism (9%), and stroke (4.5%).[27]

In addition, Sarma et al. noticed that apart from decreased LVEF (especially LVEF <31%), such parameters as atrial fibrillation, left atrial dimension exceeding 40 mm, advanced age, associated neuromuscular disease, and heart failure with dilated LV are also linked to poorer prognosis and higher mortality.[4]

Conclusions

The results of this review confirm that LVNC is not a uniform disease, but rather a cardiac abnormality encountered in different clinical situations. On the basis of this literature review we can conclude that LVNC is a cardiomyopathy associated with a variety of prognostic factors of poor outcome in terms of life threatening ventricular arrhythmia and progression of heart failure (Table 4). The prognostic factors of a poor outcome in LVNC seem to be similar to DCM and other cardiomyopathies and include the presence of atrial fibrillation, low LVEF, symptomatic heart failure, enlarged LV cavity dimension and volume, etc. In turn, its genetic connection with morbidities dependent on modifications of ion channels explains the higher probability of life-threatening ventricular arrhythmia and SCD. The higher probability of symptomatic LVNC with

Table 4. Predictors of poor outcome in patients with left ventricular noncompaction

1. mutations in genes: SCN5A, MYBPC3, TNNT2, TNNI3, MYH7 or X-linked G4.5
2. mutations in genes encoding βMHC or cTnT proteins (especially cTnT Arg131Trp mutation)
3. New York Heart Association class III–IV, palpitations, syncope, heart failure symptoms
4. late gadolinium enhancement in cardiac magnetic resonance examination
5. sustained ventricular arrhythmia, ventricular tachycardia, ventricular fibrillation
6. hospital admission due to heart failure
7. systemic embolization
8. inpatient's left ventricular noncompaction diagnosis
9. left ventricular fractional shortening <25%, left ventricular ejection fraction <31%
10. arterial hypertension
11. advanced age
12. inadequate anticoagulation
13. atrial fibrillation
14. pregnancy and post-partum period
15. left atrial dimension >40 mm
16. neuromuscular disorder
17. heart failure with dilated left ventricle
18. young age at presentation
19. cardiac and neuromuscular comorbidity
20. thin right ventricle wall in a presence of implanted cardioverter-defibrillator (ICD)
21. fragmented narrow QRS complex

SCN5A – sodium voltage-gated channel alfa subunit 5 (human); MYBPC3 – myosine binding protein C (cardiac); TNNT2 – troponin T type 2 (cardiac); TNNI3 – troponin T type 3 (cardiac); MYH7 – myosin heavy chain 7 (human); βMHC – beta myosin heavy chain (human, cardiac).

higher mortality rates in children and adolescents than in adults, as well as better prognoses in outpatients vs inpatients, may be explained by the severity and the clinical significance of the genetic and morphological abnormalities.[26] All of the above seems to vary a great deal among patients with LVNC and this is the reason patients with LVNC should undergo investigations assessing their individual risk for arrhythmia and heart failure progression and should be closely followed up.

It is also important to remember that due to the frequent association between LVNC and neuromuscular diseases, all patients suffering from LVNC should be referred to neurologists.[26] In turn, it seems reasonable to use the Cardiac Disease in Pregnancy assessment tool and perform individual exercise testing to assess the cardiovascular risk in pregnant women.[17]

On the basis of the current knowledge collected in this review, the authors consider worth pointing out the need to establish SCD-in-LVNC risk model. This can only be achieved by close cooperation between cardiologists from different health care institutions worldwide and by creating a national and later global LVNC registry. A model of this kind would probably help cardiologists properly estimate the clinical risk of an individual patient with LVNC and unify communication among cardiologists in this field.

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