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Left ventricular non-compaction cardiomyopathy: outlook and cardiac arrhythmias

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Acronyms
CMP: cardiomyopathy
HF: heart failure
ICD: implantable cardioverter-defibrillator
LV: left ventricle
LVNC: left ventricular non-compaction
PESH: programmed electrical stimulation of the heart
SD: sudden death

On-Line English & Spanish versions

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ABSTRACT
Cardiomyopathies are an important and diverse group of myocardial diseases associated with mechanical, electrical, or both dysfunctions. The left ventricular (LV) non-compaction is a familial cardiomyopathy of uncertain etiology, whose exact incidence and prevalence are unknown. It is characterized by an increase in the trabecular mass of the LV in contrast to a thin compact epicardial layer that can be visualized with imaging techniques that confirm the diagnosis. In this article is described the classification of MOGE (S) for cardiomyopathies, electrocardiographic disorders that can be found in patients with left ventricular non-compaction, the role of programmed electrical stimulation of the heart and other aspects of interest of this disease. In addition, some demonstrative electrocardiographic disorders (Stollberger and Jenni criteria) found in affected patients are presented.
Keywords: Left ventricular non-compaction, Spongiform cardiomyopathy, Cardiac arrhythmias, Classification

Ventrículo izquierdo no compacto: panorámica y arritmogenia

RESUMEN
Las miocardiopatías constituyen un grupo importante y heterogéneo de enfermedades del miocardio asociadas a disfunción mecánica, eléctrica, o ambas. El ventrículo izquierdo no compacto es una miocardiopatía familiar de etiología incierta de la que se desconocen sus exactas incidencia y prevalencia. Se caracteriza por un aumento en la masa trabecular del VI en contraste con una fina capa epicárdica compacta que puede visualizarse con técnicas de imagen que confirman el diagnóstico. En este artículo se describen la clasificación de MOGE(S) para las miocardiopatías, los trastornos electrocardiográficos que pueden encontrarse en pacientes con ventrículo izquierdo no compacto, el papel de la estimulación eléctrica programada del corazón y otros aspectos de interés de esta enfermedad. Además, se presentan algunos trastornos electrocardiográficos demostrativos (criterios de Stollberger y Jenni) encontrados en pacientes afectados.
Palabras clave: Ventrículo izquierdo no compacto, Miocardiopatía espongiforme, Arritmias cardíacas, Miocardiopatías, Clasificación

CARDIOMYOPATHIES

Cardiomyopathies (CMP) are an important and diverse group of myocar-

dial diseases associated with mechanical (diastolic or systolic) electrical dysfunction, or both, that usually exhibit inappropriate ventricular hypertrophy or dilatation, and are due to a variety of causes (often genetic). Cardiomyopathies are confined to the heart or are part of generalized systemic disorders, and often lead to cardiovascular death or progressive heart failure (HF)[1,2].

The importance of classifications

Classification systems appear in every aspect of our lives but to remain useful they must evolve with the accrual of knowledge[3]. A classification serves to bridge the gap between ignorance and knowledge[4].

Regarding CMPs, it is time to use new definitions and classifications, redefinitions and reclassifications. There is an actual revolution in the field of these complex and diverse diseases. In 1980 the World Health Organization (WHO) and the International Society and Federation of Cardiology joined efforts to establish a classification. In 1995 the WHO classified myocardial diseases associated with cardiac dysfunction, not only with depressed contractility and impaired diastolic function but also including rhythm disturbances. It was based on molecular genetics and genomics, and left ventricle noncompaction (LVNC) remained among those unclassified[5].

WHY NEW CLASSIFICATIONS? THEIR EVOLUTION

What left ventricular non-compaction is: Its place within cardiomyopathies

Cardiomyopathies have been classified as primary or secondary, according to morphological and functional criteria. The American Heart Association classified LVNC (also called spongiform myocardium, fetal myocardium, non-compacted left ventricular myocardium, hypertrabeculation syndrome, left ventricular non-compaction, spongiform CMP, left ventricular hypertrabeculation), as a different category (2006) and is included within primary CMP, genetic or not, with single or predominant cardiac involvement, hereditary heart diseases with risk of ventricular arrhythmias, complete atrio-ventricular block and episodes of sudden death (SD), with alterations in myocardial proteins and a distinctive (spongy) morphological appearance of the left ventricular myocardium. Noncompaction mostly involves the apical, mid-lateral and mid-inferior regions of the left ventricle (LV) chamber with deep intertrabecular recesses (sinusoids) in communication with the ventricular cavity, resulting from an anomalous embryogenesis. LVNC may be isolated or associated with other congenital heart diseases, may be familial or not, and overlap with hypertrophic (H), dilated (D) or restrictive CMP, suggesting a persistent disease connected with sarcomeric gene mutations, congenital heart disease and systemic neuromuscular and metabolic diseases[1,6-9]. LVNC is a rare, congenital, primary genetic disease resulting from intrauterine failure of the myocardial compaction process. Deep intertrabecular recesses in intensely hypertrophied and often hypokinetic segments of the LV myocardium are characteristic of this cardiomyopathy. Heart failure, embolic events, arrhythmias, and SD are associated to LVNC[9]. Echocardiogram and magnetic resonance imaging are the diagnostic procedures of choice[10].

LVNC is a familial CMP (its exact incidence and prevalence are unknown), of uncertain etiology for which a genetic origin has been proposed[6,7]. From the anatomopathological point of view, it is characterized by an increased LV trabecula (non-compact) in contrast to a thin epicardial compacted layer that can be visualized with imaging techniques that confirm the diagnosis[10,11].

Typically, the LV is smooth inside, except for the two papillary muscles (anterior or lateral, and posterior or medial), where the tendinous cords of the mitral valve are attached. There are no muscular trabeculae dividing the cavity into different segments like in the right ventricle[2].

The myocardium in LVNC may show normal or abnormal systolic and diastolic function, it may present with ventricular dilatation or hypertrophy, and its size and function may change unexpectedly (undulating phenotype)[6]. People on chronic treatment for compensating HF occasionally present with an acutely HF worsening.

This disease has been considered as a syndrome, not always genetic. Others consider LVNC a genetic or mixed CMP[12]. In 2006 LVNC was recognized as a genetic CMP (American Heart Association), whose nomenclature and pathogenesis are characterized by a thickening of the regional ventricular wall and deep trabecular recesses. Its genetics may overlap with phenotypes of other genetic or mixed CMPs (D-

CMP, H-CMP and others), with pathological and pathophysiological variations of the myocardial architecture and its function. Due to different causes and pathophysiological mechanisms, the ventricular myocardial structure development may be complex and chaotic. There is a morphological trait of the myocardial structure with a wide spectrum of normal variants to the pathological phenotypes of LVNC, which reflect the embryogenic structure of the human heart due to an arrest in the compaction process during the first trimester, with or without other congenital heart malformations. There is a complex genetic, etiological, symptomatic and pathological diversity also expressed in diagnostic imaging, with myocardial development variations related to gene mutation and phenotype of one or a group of genes, by interacting processes and disturbed gene modulation, functional and other expressions.

The first LVNC case was described in 1926 after an autopsy performed on a newborn with congenital heart disease, and by echocardiogram in 1984. It has become recognized since then. Anyway, it is discussed whether LVNC is a separate CMP or a phenotypic morphological character shared by different CMPs[13].

The extraordinary advances in molecular genetics in recent years have propelled new classifications that seek to be more accurate, rigorous, open to coming advances in the era of biology and molecular genetics of cardiovascular diseases, but they should also be simple, clear and flexible.

LVNC is a rare disorder of endomyocardial morphogenesis characterized by multiple trabeculations in the left ventricular myocardium. Literature suggests that LVNC is rare in adults and is associated with a poor prognosis. As this alteration may be present from birth, several studies consider it a familial disease, asymptomatic in some patients. Murphy[14] hypothesizes that LVNC has a long pre-clinical phase and that prognosis is unrepresentative of its true natural history.

During normal embryonic development, endomyocardial trabeculations emerge from the apical region of the primitive ventricles around day 32 of fetal life, through a process of resorption and remodeling. The myocardium begins as a loose mesh of muscle fibers that gradually condenses from epicardium to endocardium, resulting in compaction of the endocardial surface between the fifth and eighth week of fetal life, more complete in the LV than in the right ventricle. Arrest in normal endomyocardial morphogenesis causes LVNC and represents a defect in the compaction process[13,14].

The histologic examination evidences continuity between the LV endocardium and the deep intertrabecular recesses, suitable for substrate formation for which enables the propagation of reentrant arrhythmic circuits[15].

During normal embryological development, the heart is a spongy meshwork of muscle fibers and trabeculations separated by recesses; before the coronary vessels develop, these intertrabecular recesses, or sinusoids communicate with the cavum of the ventricle to receive blood supply. After coronary development, the ventricular myocardium gradually becomes compacted and the recesses become capillaries. Trabecular compaction occurs between 12-18 weeks of gestation, starting from the base to the apex. This process does not occur in LVNC leading to the development of a thickened, non-compacted endomyocardial layer with prominent trabeculae that are continuous with the LV cavity and lack communication with the epicardial circulation, with deep recesses and a thin compacted epicardial layer, lacking non-compacted myocardium regression[16].

Genomic and molecular orientation facilitate interaction between the clinical appearance and research, and among the complex genotype-phenotype relationships. This opens new ways to assess molecular genetics of myocardial disease, while allowing the inclusion of recently described alterations and their inclusion to the complex and heterogeneous field of these diseases, which have received different classifications over time. This allows genetic arrhythmic diseases (more frequently than thought and an important cause of SD), to be comprised into CMPs, enlarge the list of hereditary arrhythmic manifestations and incorporate diseases recently described or better known now, such as ionic channelopathies[16].

LVNC is included among those CMPs not classified by the World Health Organization and the European Society of Cardiology, and as a genetic CMP by the American Heart Association [4,16,17].

The MOGE(S) classification describes the phenotype, the involvement of other organs as «red flags», and genetic cause or not of the disease (**Table 1**)[10, 18].

The «M» notation provides a descriptive diagnosis of the phenotype, but there may be overlapping phenotypes with clinical markers (for example, atrioventricular block, Wolff-Parkinson-White and others), and organ involvement (O) solely of the heart,

Table 1. MOGE (S) classification of cardiomyopathies [3,10,18-20].

M	O	G	E	(S)
Morphofunctional characteristics (phenotype)	Organ involvement	Genetic or familial inheritance pattern	Etiology (details of genetic defects or underlying disease, cause/substrate)	Status (funcional)

This classification discriminates LVNC with left ventricular dilation and dysfunction (M_{LVNC+D}) or with hypertrophy (M_{LVNC+H}), from pure left ventricular non-compaction (LVNC)[10].

or not. The «E» offers essential information for the type of CMP (familial, patient, genetics).

It is a descriptive nosology that combines morphofunctional trait and organ-system involvement with familial inheritance pattern, and identifies genetic defect or other causes. The introduction of the concept of diagnostic «red flags» by Arbustini *et al.*[10] is revolutionary for clinical geneticists, with clinical markers that can guide the genetic research to a specific gene. This new classification is more detailed with respect to the previous American and European attempts. This approach may be useful for inherited CMPs, but it is difficult to apply to arrhythmogenic right ventricular dysplasia because even the epsilon wave, many years considered the marker of the disease, can represent a «red flag» only when it is present in the electrocardiogram, and diagnosis requires several of these red flags[10].

This system allows us to approach the unresolved problem of the phenotype-genotype correlation, considering families carrying the same mutation, but only in this case will be possible to use the genetic data for the prognosis and therapy of inherited CMP, although it is well-known that many mutations are unique[18,19].

Most cardiomyopathies are familial diseases. Family screening identifies asymptomatic patients and relatives with early traits of disease. For the last 50 years, CMPs classifications have been based on the morphofunctional phenotypes, allowing cardiologists to conveniently group them in broad descriptive categories. However, the phenotype not always conforms to the genetic characteristics. It may not allow risk stratification, and may not provide preclinical diagnoses in the family members. More genetic testing is are being carried out nowadays, which is already a part of clinical work-up. Based on the genetic heterogeneity, new names are being coined for the description of CMPs associated with mutations of different genes; that is why a comprehensive nosology is required for informing the clinical phenotype and involvement of organs other than the heart, as well as the genotype and the mode of inheritance. The recently proposed MOGE(S) nosology system embodies all of these characteristics and uses the criteria of the American College of Cardiology/American Heart Association and the functional class of the New York Heart Association. This nomenclature is supported by web-assisted applications and helps to describe symptomatic/asymptomatic or familial CMPs in the context of genetic testing. It is flexible, allows its expansion, helps to understand its etiological bases and describe the genetic complexes, and also ensures records completeness[20].

A possible limitation of MOGE(S) is the lack of information about one of the most important clinical issues in CMPs: arrhythmias. Although their classification of arrhythmias is not the aim of MOGE(S); an expansion of the «S» has been proposed to include rhythm disturbances. The committee in charge of this classification is working with electrophysiologists to quickly develop a clinically-useful description of rhythm disturbances as a second «S»[21].

This nosological system seems to be a complex and complicated in clinical practice, but it would be rather simple if progressive steps are applied and does not obligate a clinician to include genetic testing. Other advantages are described in **box**[21].

The Arbustini *et al.*[10] system is flexible and adaptable as it links etiology with clinical phenotypes and, by inference, delves into treatment and prognosis. The term «cardiomyopathy» refers to any disease of the myocardium that is not explained by coronary artery narrowing or abnormal loading of the ventricles. These disorders arise from within the cardiomyocyte or the extracellular matrix. Clinicians have grouped CMP into subcategories on the basis

of ventricular morphology and function. This approach aligns very closely with clinical presentation and therapeutic strategies, but it is limited by not considering etiology or excluding mild or intermediate phenotypes that do not meet conventional diagnostic criteria. The aforementioned system[10] attempts to capture the pathophysiological complexity of CMPs representing a logical progression in the diagnostic pathway proposed in recent meetings of the European Society of Cardiology in which conventional cardiological assessments are combined with noncardiac and molecular parameters to approach diagnosis. Clinical features groups or diagnostic «red flags» can be used to identify specific genetic CMP subtypes that require individualized management and treatment strategies, but we must consider the morphofunctional class (M) which attempts to summarize informative phenotypic characteristics and diagnostic clues, such as atrioventricular block and others.

Box. Other advantages of the MOGE(S) classification[21].

- Considers family history and SD.
- Establishes a hierarchical: phenotype → organ-tissue involvement → genetic/familial → etiology-gene.
- Allows for better understanding of the genetic basis of CMP.
- Calls for a standardized, universally acceptable classification with a system that integrates both phenotype description and genetic information.
- Facilitates the transition of CMPs description from the pre-genetic to the genetic era.
- Ensures to capture great amounts of data that could be lost if not systematically registered.
- -Compels to describe the results achieved in all diagnostic steps (clinical-cardiologic and extracardiac evaluations, clinical genetics, family screening, molecular genetics when possible, functional status), providing a uniform language and identical information.

CMP, cardiomyopathy, SD, sudden death

The system has come in for some criticism: whether it is an early disease, or the same criteria have not been adopted, or data is still unspecified. Although it is recognized that it represents a bridge between the new disciplines (such as proteomics and genomics) and clinical medicine, with diagnostic and prognostic utility yet to be defined[3]. It is necessary to integrate basic sciences and clinical medicine. According to Elliott[3], Paul Wood in 1950 said: "...I have attempted to maintain a proper balance between man and his instruments, between experienced opinion and statistics, between traditional views and heterodox, between bed-side medicine and special tests, between the practical and the academic, and so to link the past with the present".

LVNC is a primary CMP with a specific morphological pattern presenting a two-layer myocardium structure: a thin compacted epicardial layer and a markedly thickened non-compacted endocardial layer, consisting on trabecular meshwork with deep endomyocardial spaces occurring in the absence of other coexisting congenital anomalies[22].

Regarding the phenotype and the genotype, an overlap of the LVNC can be found with other CMP; there is no characteristic histology to confirm its diagnosis by means of imaging; all the diagnostic criteria try to describe the particularities of a three-dimensional, complex and random affectation, from two-dimensional images; there is no gold standard to compare these cases and detailed trabeculation characteristics in a normal heart are not well known, as well as the mild phenotypes that can be found in a disease that seems familial.

LVNC may be sporadic or familial (mitochondrial, cytoskeletal and sarcomeric protein mutation). Healthy individuals may fulfil imaging criteria for diagnosis and children may present sudden infant death syndrome. As seen in families with H- or D-CMP, doubts arise as to accepting it as a different disease. The extent of myocardial compaction may be a trait within the population and imaging techniques detect subtle variations in morphology within the normal range, not as a root cause of myocardial dysfunction. LVNC may be secondary to a genetic alteration well-tolerated when the heart is normal. But more restricted diagnostic criteria are required. That is, there is doubt as to whether LVNC is a cause, contributor, or epiphenomenon in these patients. In the presence of a genetic mutation, disruption to myocyte function at a molecular level may be the primary disease determinant with ventricular noncompaction, arising as a maladaptive remodelling response combining the primary disease to subendocardial ischaemia and fibrosis[23].

Left ventricular non-compaction: Electrocardiogram and arrhythmias

These patients may present with a broad clinical spectrum, from the discovery of the disease in asymptomatic individuals to those that develop life-threatening ventricular arrhythmias, left/right HF or both, and systemic embolic events[6,22]. Symptoms may be induced by exertion or persist at rest. Steffel[22] studied 78 patients who presented intraventricular conduction disorders (especially left bundle branch block), signs of left ventricular hypertrophy and abnormal repolarization. The 13% had normal ECGs (younger subjects, less HF and milder structural heart disease). In general, no specific ECG findings are found, although −usually− no systematic analysis of electrocardiogram is performed. There is a striking overlap between left bundle branch block in particular, atrial conduction delay, prolonged PR interval or atrioventricular block, prolonged QT interval, reduced systolic LV function and LV/left atrial dilatation. Patients with signs of left ventricular hypertrophy more often presented with systemic embolic events. There was a mortality of 35% during 44-months follow up, (half of cases because of sudden cardiac death), tachycardia occurred in 41% and an abnormal ECG was found in 94% of patients, with conduction block (left or right bundle branch block) as well as repolarization abnormalities being the most frequent findings.

Steffel[22] achieved a correlation between ECG and symptoms: HF, intraventricular conduction delay (especially left bundle branch block), atrial conduction delay, ventricular tachycardia/fibrillation, asystole and Wolff-Parkinson-White (possibly due to interruption of the normal process of fibrous annulus development). Twelve patients with LVNC received an implantable cardioverter-defibrillator (ICD) as primary or secondary prevention in cases of potentially lethal arrhythmias; some underwent programmed electrical stimulation of the heart (PESH) for risk stratification. Intraventricular conduction disorders were found in (50%), abnormal repolarization manifested as negative T wave in precordial leads (70%), long QT interval (50%), LV hypertrophy (30%) and normal tracings (5%)[11,22].

Duru and Candinas[24] reported a case with different clinical ventricular tachycardias that were not reproduced in PESH. Antiarrhythmic drugs, anticoagulation, pacemakers, ICD (episodes of SD), ablation, myocardial resynchronization, gene therapy and even transplantation, due to progressive LV dysfunction, have been required[11].

LVNC may be asymptomatic for years or develop D-CMP and HF, syncope, embolism, supraventricular and ventricular arrhythmias (extrasystoles, tachycardia and fibrillation), and SD[11,14,25]. Murphy *et al.*[14] studied 45 patients with LVNC to define prognosis and family incidence, and found abnormal ECG (91%), LV dilatation (66%), non-sustained ventricular tachycardia (20% in Holter monitoring) and thromboembolism (4%). They noticed a better prognosis than that previously reported and others of their results were: left bundle branch block (29%), pathological Q wave (9%), poor R-wave progression (7%), ST segment changes (9%), T wave inversion (16%) and atrial fibrillation. Pacemakers were implanted in some cases and ICD in other. The latter as a therapeutic option in the case of symptomatic arrhythmias or low ejection fraction, sudden cardiac death, syncope, sustained arrhythmias, and nonsustained ventricular tachycardia associated with syncope.

There are not many long-term follow-up data in patients with ICD, both in primary prevention (with no documented lethal arrhythmias) and in secondary prevention[15]. There is a high prevalence of supraventricular arrhythmias, atrial fibrillation and flutter (8 out of 12 patients studied by Kobza *et al.*[15]); ventricular tachyarrhythmias (38-47%) and sudden cardiac death (13-18%). The choice of ICD depends on clinical factors, rate of ventricular tachycardia and supraventricular arrhythmia, symptoms, concomitant pacing indication, signs of HF, low ejection fraction, QRS interval ≥ 120 ms, and two or three additional criteria for dyssynchrony: aortic preejection delay of more than 140 ms, interventricular mechanical delay of more than 40 ms or delayed activation of the posterolateral LV wall. In general, these are series of few patients, with no control group and short follow-ups.

The important thing is that LVNC is a highly arrhythmogenic substrate, Yin[12] reports ventricular arrhythmias in 13% and atrial flutter/fibrillation in 20% of cases.

In patients with familial LVNC, Murphy *et al.*[14] found that family members had more D-CMP than LVNC and highly symptomatic cases with a high incidence of ventricular arrhythmia and progressive HF have been reported[14].

Patients with LVNC may have a more favorable prognosis than previously described because in the family presentation there is a spectrum of abnormalities that overlap with the D-CMP and it is suggested that these diseases share a common etiology. Many

patients in the Murphy study had a mild phenotype with a lower mortality incidence, embolism or documented ventricular arrhythmias. This can be explained by a selection of subjects and screening, and because improved echocardiographic diagnosis facilitates the detection of asymptomatic cases, not previously identified. LVNC was detected retrospectively in patients diagnosed with D-CMP, this suggests that its frequency in the HF population may be underestimated as the result of inadequate imaging of the apical segments of the LV and would increase with improving cardiac imaging. In addition, there is a period of silent gestation before the onset of clinical disease and it is even discussed whether LVNC is a sub-type or variant of D-CMP rather than a distinct CMP[14].

Celiker[9] studied 11 children with LVNC and rhythm abnormalities: palpitations, syncope, bradycardia, ventricular arrhythmias, sinoatrial and atrioventricular node disorders, Wolff-Parkinson-White syndrome (in this one, due to an arrest on continuity of regression of anatomic and electrical atrioventricular embryo development).

Ikeda[16] states that the diagnosis of LVNC is more frequent nowadays, but diagnostic problems persist and the therapeutic procedure will be done according to the clinical manifestations, which is why multicenter registries are required for a better understanding of these aspects, in addition to imaging and genetic study advances. The spectrum ranges from asymptomatic to severe subjects, with variable phenotypic expressions of other CMP, and with an initial mortality of 35-47%, death or transplantation (26%), ventricular tachycardia (2-62%) and sustained/non sustained ventricular tachycardia on Holter monitoring (27%).

Brescia *et al.*[13] studied 242 children over 1990-2009 and reported: mortality 12.8%, abnormal ECG 87% (LV hypertrophy and abnormal repolarization being the most frequent), arrhythmias 33.1%, SD 6.2% and ventricular tachycardia 17.4%. Other findings were: T wave inversion, ST-segment abnormalities, atrial enlargement, left-axis deviation, prolonged QT interval, pre-excitation, atrial tachycardia and other supraventricular arrhythmias, atrial fibrillation/flutter, and accelerated junctional rhythm.

Arrhythmogenesis in the LVNC can be explained by dispersion of repolarization, myocardial ischemia and genetic causes, within a heterogeneous population and with the possible existence of subtypes (normal, dilated, hypertrophic or mixed), whose spectrum ranges from a high mortality with progressive myocardial dysfunction, to low risk of SD when heart size and function are normal.

Stollberger *et al.*[26] studied 105 patients (1995-2011) in whom LVNC was associated with neuromuscular diseases. They analyzed ECG abnormalities and reported: ST-segment and T-wave abnormalities, left anterior fascicular block, atrial fibrillation, widening of the QRS complex, abnormal Q waves, intraventricular conduction disorders, LV hypertrophy, low voltage, right/left branch block, prolonged PR interval, prolonged QT interval, sinus tachycardia and, above all, they detailed the evolutionary changes of these disorders. However, one wonders how much sould be attributed to LVNC and how much to associated neuromuscular disorders.

Some uncertainty remains about the natural history of LVNC because studies are small, but in any case, Viskin and Rogowski[27] make reference to the «discoverer's effect», and claim that initial descriptions of H-CMP from tertiary centres portrayed a very grim prognosis. Later, with newer community-based studies, a more balanced and less ominous picture was recognized. A similar phenomenon was subsequently documented in Brugada syndrome. On the other hand, symptomatic cases are reported more often (those more serious and complex), while diagnosis ignores asymptomatic LVNC. When describing a recently known disease, morbidity and mortality are often overestimated. Over time, asymptomatic patients are better identified and a more realistic perception of the problem is achieved, which is known as the «discoverer's effect»[27].

THE ROLE OF PROGRAMMED ELECTRICAL STIMULATION OF THE HEART

PESH can be useful and have some predictive value in symptomatic or syncopal arrhythmias, distinction between supraventricular or ventricular disorders and treatment, relationship with low ejection fraction, prevention of sudden cardiac death and syncope, or any unknown cause with depressed LV function or structural heart disease. Although its role for risk stratification is discussed, or left out, Kobza[15] used PESH –with an aggressive protocol– in patients with LVNC, at three basic cycle lengths 500, 400 and 330 ms, and up to 3 extrastimuli, with a minimum coupling interval of 180 ms, from the right ventricle apex and the outflow tract.

PESH, as we see it, is useful in various diseases but does not have the last word as it was thought years ago; at present, their results should be considered in another level. PEPH has limitations and this should be considered. Several things may happen (**Figure 1**):

- The same clinical arrhythmia may not be reproduced in the laboratory.
- An artificial (laboratory) or preclinical arrhythmia may be originated.
- Reproducing clinical arrhythmia that, later, will not appear in real life or vice versa, not being reproduced but appearing later.
- Being an automatic arrhythmia or –if also– reentrant the three elements of the triangle do not coincide (substrate, trigger and modulator) and, therefore may be irreproducible.

It must be given its real prognostic value and be cautious when chosing on a therapy (for example, ICD), based on PESH outcome. On the other hand, in some situations arrhythmias are poorly reproducible in the electrophysiology laboratory. The procedure must be given its true value, knowing its variability from one moment to the next in the same patient and the existence of specific and nonspecific responses[28,29]. It would be convenient to read and analyze two fundamental works by Josephson[30,31] to find out what is left for PESH in the ICD and ablation era, articles with 10 years apart, in which the cardiac electrophysiology is considered to be in a crossroads, lacks today critical thinking, basic understanding and is in crisis of credibility. Josephson says: "If one asks me where we go from here, I would respond: back to basics learn-electrophysiology"[30,31]. It is essential to know what we should or should not expect from PESH. Practicing some procedures emerges as a trend at times, and therapeutic decisions are based on them and therapeutic decisions are based on them. We must know what was done in the past and what should be done now: not to replace electrophysiology with electrotechnology, which must go hand in hand, as electrocardiography and electrophysiology should do.

Fifty years after PESH was established as a clinical procedure, several of its indications and concepts have changed and some of its limitations are now evident (although still a fundamental tool for arrhythmology). The function of the electrophysiology laboratory changed from the diagnostic and artistic to the therapeutic par excellence, although there must be an absolute connection in both senses: the understanding of arrhythmic substrates and their ablation; electrophysiology and electrotech-

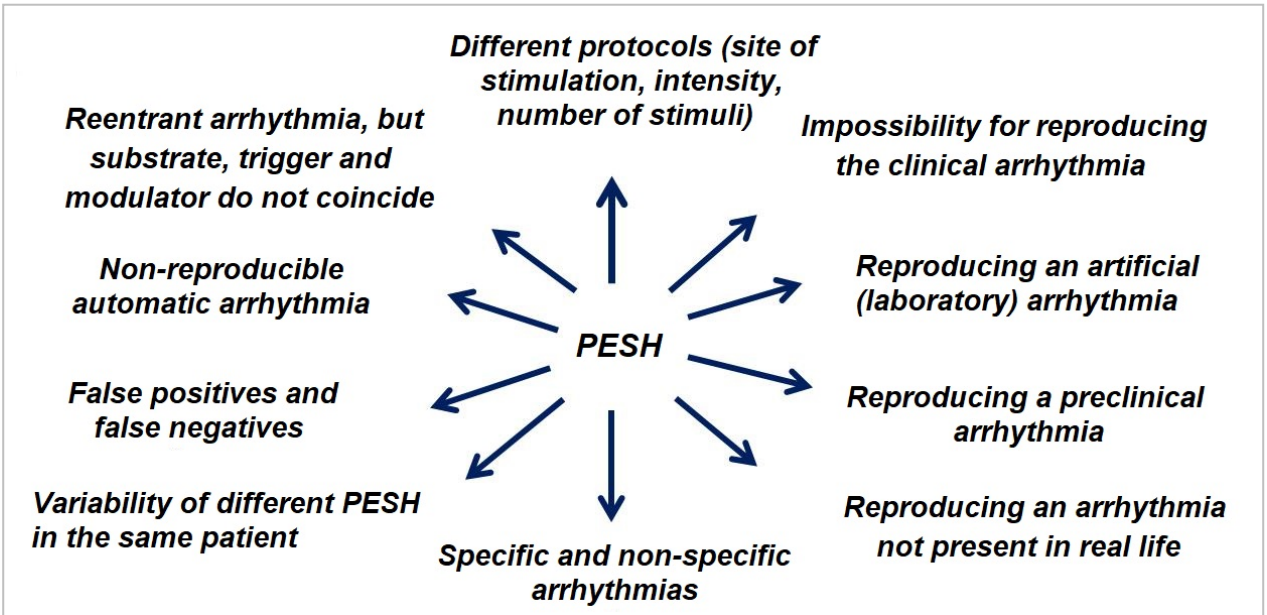

Figure 1. Programmed electrical stimulation of the heart: conflicts to stratify the risk of malignant ventricular arrhythmias. PESH, programmed electrical stimulation of the heart.

nology should not be divorced as they enhance each other. PESH should be given its true place as it uses artificial triggers that may not match symptom or that control modulating elements (only the autonomic nervous system in a limited way), and delve into the triangle of any reentrant arrhythmia: the arrhythmogenic substrate, the trigger or triggering element and the modulating factor, to be fully inserted in the arrhythmic process, without forgetting the possible variability of an electrophysiological study to another in the same patient.

The fact that this subject has been so largely discussed and published, and the many contradictory opinions among prominent researchers, indicates that it is an unresolved problem. Initially, PESH played a preeminent role in risk stratification and was granted the highest reliability for therapy choices, then all of this returned to normal and, while accepting its contribution, we know that PESH may not always say the last word. Over time, several questions have arisen: what is its true utility for risk stratification? How much would PESH influence on ICD implantation? To what extent inducing a malignant ventricular arrhythmia in the laboratory may be beneficial to predict the debut or relapse during follow-up? Reservations and limitations continue on. There are things yet to be defined concerning protocols, registries, false positives and negatives, and stimulation sites[28,29,32].

Even when coping with dissimilar conditions, let us recall some very discussed points on LVNC and Brugada syndrome in terms of conceptual problems related to PESH and other aspects: the uncertain role on risk stratification and therapeutic decisions, the existence of signs and syndromes or signs possibly evolving into syndromes, the overlap of other channelopathies to Brugada syndrome, and also the overlapping of other CMPs to LVNC, the wide clinical spectrum that ranges from asymptomatic subjects to the most serious, and the clues for an underlying organic disease in Brugada syndrome[28,29,33].

OTHER ASPECTS ABOUT LEFT VENTRICULAR NON-COMPACTION

Many questions remain to be defined regarding LVNC, Arbustini refers to them in his 2014[21] article: whether it is a different CMP or a morphological character shared by several CMPs. Several strategies have been discussed for the diagnosis and treatment of LVNC patients in terms of embryology, basic mechanisms, epidemiology, anatomy, pathology, clinical manifestations, images, therapeutic and genetic modalities[34,35]. The three markers for LVNC are: prominent trabeculations of the LV, deep intertrabecular recesses and thin compacted layer. Although genetic data from mice and humans support LVNC as a distinct CMP, evidence for LVNC as a shared morphological trait is not ruled out. Better imaging interpretation and genetic advances lead to a greater overall understanding of its basic mechanisms and optimal management. The spectrum of morphologic variability is particularly wide, ranging from hearts with a nearly absent compacted layer and an exclusive trabecular component in the LV apex, to hearts with prominent trabeculae and deep alternating recesses but having a well-represented compacted layer. LVNC may be isolated or associated with CMP, congenital diseases and complex syndromes involving the heart. The American Heart Association classifies LVNC as a genetic CMP, whereas the European Society of Cardiology includes LVNC as an unclassified CMP, as does The World Heart Organization's International Classification of Diseases.

Left ventricular non-compaction may be familial (inherited) or not (sporadic, if proven absent in relatives), acquired, as in high-performance athletes, sickle cell anemia patients and pregnant women (sometimes the trabecular phenotype may occur due to a mechanical load and disappear as it dissipates during post-partum). It is not known whether, in these cases, there is a genetic underpinning to the disease. The 75% of children with ECG abnormalities and death have depressed systolic function. Some have transient recovery followed by deterioration, which suggests a genetic nature. Most familial cases are associated with mutations in the same genes that cause other types of CMP. Whether these genes cause CMP or is triggered by some phenotype is not entirely clear. Although there is no gold standard for LVNC diagnosis, imaging is the best tool and is related to the pathological anatomy findings (during autopsy or transplantation): echocardiogram is compulsory and magnetic resonance imaging offers anatomic and functional details. Clinical management of patients with LVNC is based on the functional phenotype and complications. In the case of arrhythmias, the options are: devices, ablation of LV focus, resynchronization and LV surgical remodeling.

Given the multiple etiologic bases of LVNC, it can

be seen as an isolated trait or disease in association with genetic diseases and congenital defects; sporadic or acquired in physiological or pathologic conditions; permanent or transient; or originated during embryonic development (embryogenic hypothesis). Cardiac trabeculation starts after the cardiac looping stage. Trabeculae formation begins with the emergence of myocytes through delamination (migration) from the compacted myocardium. Dilatation and LV hypertrophy may or may not occur.

By itself, LVNC does not necessarily describe a disease, it can be an anatomic variant of LV structure and its differential diagnosis includes prominent hypertrabeculation with normal compacted LV layer, apical H-CMP, D-CMP, endocardial fibroelastosis and LV apical thrombus. When LV size and function are normal only clinical monitoring may be required; if there are symptoms due to dilation, dysfunction or hypertrophy, treatment will depend on HF, arrhythmias and phenotype (genetic tests do not modify it).

Complications such as HF, arrhythmias (atrial fibrillation, ventricular tachycardia in 47% of symptomatic patients), sudden cardiac death events (13-18%), systemic embolic events and others may occur. There are still things to be defined in the future: whether LVNC is a primary disease, or occurs isolated or in association with another CMP; whether it is clinically useful to indicate the CMP phenotype and the LVNC (H-CMP, restrictive CMP, D-CMP, arrhythmogenic right ventricular CMP), to discriminate LVNC from isolated LVNC with normal LV size and function; its role as a clinical marker and the diagnostic genetic hypothesis. In general, reproducible and unified diagnostic criteria (based on imaging and world registers) are required, as well as data on outcomes in LVNC patients, along with a wide-ranging collection of cases, imaging records and genetic information[21].

As for treatment, the precise diagnosis of the phenotype must be achieved through the different outcomes and the various procedures to be used. In inherited LVNC, first degree relatives (who generally have not undergone imaging techniques) can undergo screening, and genetic tests may affect the course of action, which varies according to myocardial dysfunction, arrhythmias, or congenital heart disease, with several options: anticongestives, angiotensin-converting enzyme inhibitors, beta-blockers, aldosterone antagonists, diuretics, vasodilators, aspirin, inotropes, ICD, cardiac resynchronization therapy, transplantation, calcium blockers, antiplatelet therapy or anticoagulants, as well as other treatments with vitamins, coenzymes, carnitine, percutaneous catheterization procedures or surgery[36].

There are several LVNC subtypes, with at least 8 different phenotypes, with dissimilar treatments and outcomes (**Table 2**)[36].

As mentioned before, LVNC usually has an abnormal ECG. The 87% present with hypertrophy (LV or biventricular) by voltage criteria, T-wave inversion, ST-segment abnormalities or overload, left atrial enlargement, left-axis deviation, prolonged QT interval or pre-excitation. QRS voltage may be extreme in neonates and young children.

Arrhythmias are supraventricular and ventricular, there may be bradyarrhythmias, life-threatening in many cases. The subtype with early rhythm abnormalities courses with risk of SD. ICD is very effective in preventing arrhythmic SD, including those with severe LV dysfunction, previous history of supraventricular tachycardia or fibrillation, unexplained recurrent syncope, or family history of sudden cardiac death. Ventricular tachyarrhythmias (including patients with ventricular fibrillation causing cardiac arrest) are reported in 38-47% of adults with LVNC, and in 13-18% of those who die suddenly[36].

A series of 77 adults reported that 44 of them were implanted an ICD (by the standard guidelines for non-ischemic CMPs), with an average 33 months' follow-up, 8 had appropriate shocks after 6 months (median), which suggests that the LVNC has a high risk of sudden cardiac death. Appropriate shocks are associated with ventricular tachycardia, although the initial rhythm is sometimes unknown in patients with sudden cardiac death (ventricular fibrillation triggered by ventricular tachycardia)[36].

In patients with LVNC and sustained ventricular arrhythmias, recurrences with appropriate shocks were 33% at a mean 26 months' follow-up. Appropriate shocks have also been reported in 37% of patients with LVNC and ICD in a 40-month follow-up. In young children, antiarrhythmic drugs can be prescribed before ICD due to the high frequency of electrode fractures and inappropriate shocks in that population[36].

Adults may have a high risk of ventricular tachyarrhythmias and episodes of sudden cardiac death, 47-74% of symptomatic patients die within 6 years of presentation. More recent researches speak of a more benign natural history, with lower risk of ventricular arrhythmias. In a study of 241 adult patients with isolated LVNC, there was a 6.2% of cardiovascu-

Table 2. Left ventricular noncompaction subtypes [36].

LVNC Subtype	Characteristics
Benign	LV size is normal and the thick wall presents preserved systo-diastolic function; in 35% of patients, benign CMP is a predictor for good outcome in the absence of clinically significant arrhythmias. It has been said, by this subtype, that LVNC does not represent a CMP but a normal and benign variation, with similar outcome to that of the general population. Severe forms tend to occur in childhood and patients with successful treatment (transplantation) or death do not reach adulthood to see a cardiologist.
Dilated	Presents with concomitant LV dilation and systolic dysfunction; the so-called undulatory phenotype may occur during the course of disease, the LV is smaller with slight wall hypertrophy and functioning improves before dilatation. D-CMP outcome is similar to that of individuals with no LVNC with some D-CMP involvement. In neonates and infants is worse than in other types of D-CMP.
Hypertrophic	LV thickening is typically seen with asymmetric septal hypertrophy, diastolic dysfunction and hypercontractile systolic function. Occasionally, LV dilation occurs with late systolic dysfunction during the course of disease. Outcome resembles that of general population or to those with a similar degree of H-CMP with no LVNC.
Hypertrophic dilated	Mixed phenotype with LV thickening, dilatation and depressed systolic function. It is associated with an increased risk of death and with metabolic or mitochondrial disease in children. It is the most common undulating phenotype and results in a dilated LV with poor functioning and low cardiac output. This subtype has a worse prognosis than other mixed phenotypes like some H-CMP.
Restrictive	Infrequent, characterized by left/biatrial enlargement and diastolic dysfunction, resembles restrictive CMP presentation and patients have a poor outcome (arrhythmias, SD and heart failure with preserved ejection fraction are less frequent), its prognosis is similar to analogous forms of restrictive CMP.
Right ventricle or both	Hypertrabeculations are seen in both ventricles. There are no standard diagnostic criteria and diagnosis of LVNC may be suggested, prominent trabeculations of the RV wall and hypertrophy, robust in severe cases, with significant spongiform appearance. Possible implications are unknown.
With congenital heart disease	Association with almost all congenital heart diseases may contribute to myocardial dysfunction, arrhythmias or both. Right-sided anomalies are the most frequent, especially pulmonary stenosis, Ebstein's disease, and pulmonary and tricuspid atresias. Septal defects and left-sided congenital diseases may be present. Prognosis depends on the type of congenital heart disease. LVNC increases postoperative risk and ventricular dysfunction worsens outcome.
With arrhythmias	The specific substrate for the development of malignant ventricular arrhythmias is unknown. Systolic function is preserved, and LV size and wall thickness are normal. Associated arrhythmias usually permit diagnosis. These ventricular arrhythmias are an independent risk factor for mortality and many are not detected, being cases with worse evolution than the general population or with similar forms of arrhythmias without LVNC[36].

CMP, cardiomyopathy; D-CMP, dilated cardiomyopathy; H-CMP, hypertrophic cardiomyopathy; LV, left ventricle; LVNC, left ventricular non-compaction; SD, sudden death.

lar death with associated measures (transplant, ICD) and an 8.6% of cardiovascular events (death, stroke, ICD shocks, transplantation)[36].

Ventricular arrhythmias in the LVNC have been related to: microreentry in the trabeculated myocardium, epicardial coronary hypoperfusion and concurrent developmental arrest of the conduction system. It has been suggested that premature ventricular contractions in this disease mostly originate in the conduction system and myocardial areas, and not in the echocardiographic areas affected by noncompaction. Van Malderen *et al.*[37] studied 101 patients with LVNC to determine the origin of extrasystoles, they compared each origin site with the

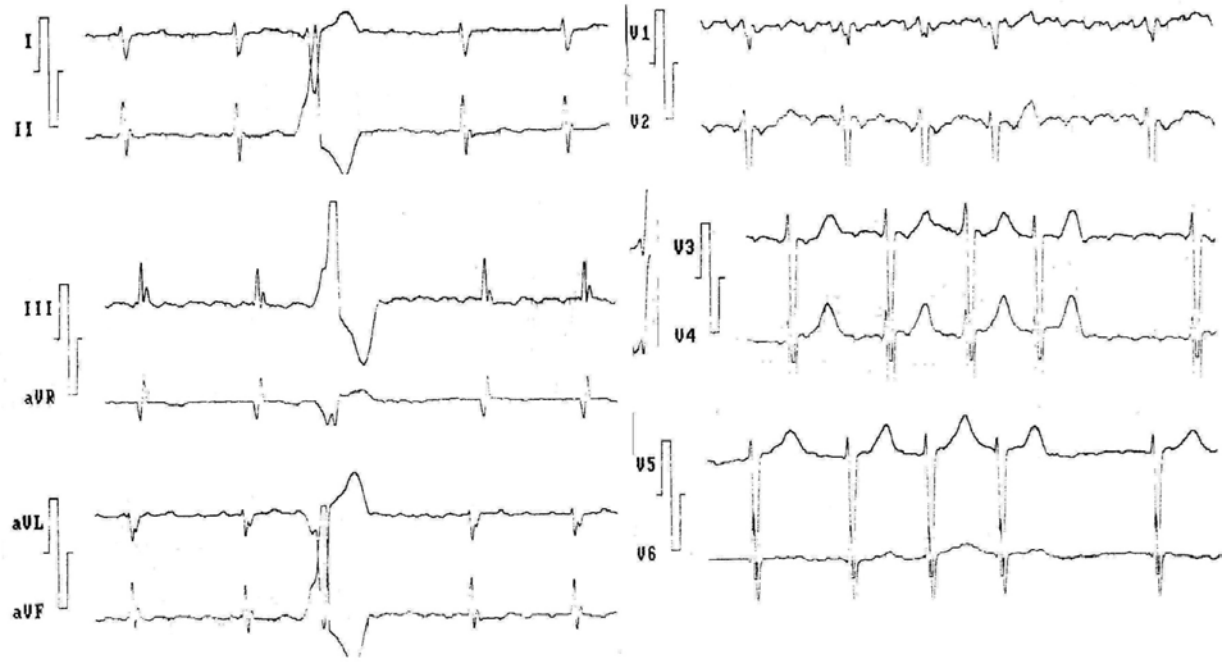

Figure 2. Patient with left ventricular noncompaction who meets Stollberger and Jenni criteria [28,43]. The electrocardiogram shows atrial flutter with variable atrioventricular block and premature ventricular complexes.

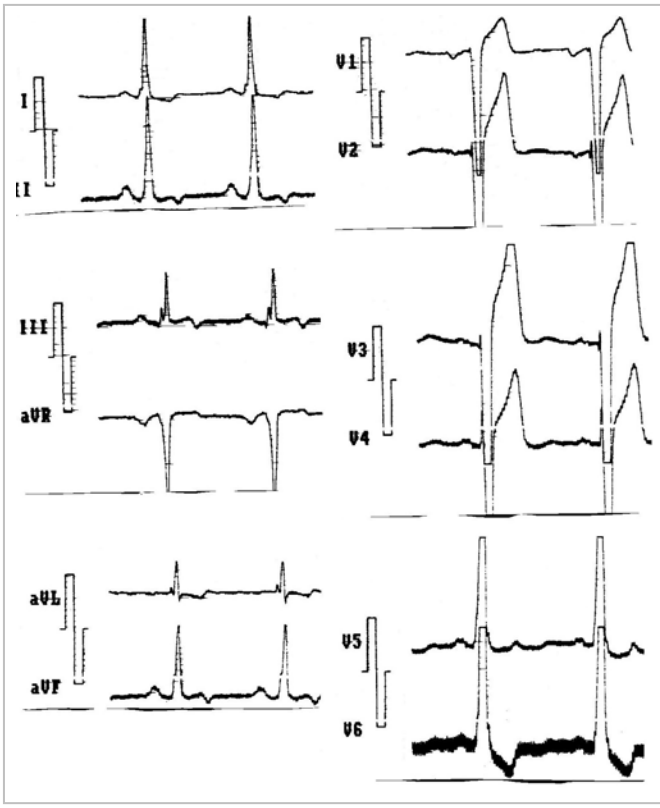

Figure 3. Man with left ventricular noncompaction that meets the criteria of Stollberger and Jenni[28,43]. Sinus rhythm, notching on the ascending branch of the R wave (D_I, D_{III}, aVL); negative T wave in D_{II}, D_{III}, aVF and V_6. There is almost no ST segment in precordial leads V_1-V_4. T wave peaking in leads V_2-V_4. Enlarged left ventricle. QT interval 300 ms, cQT 344 ms. Viskin[41] specifies the following values for corrected QT in men: 360-390 ms, normal; 330-360 ms, short; and less than 330 ms, very short. In this patient, a short QT interval is possible. We did not find (in the reviewed literature) this finding in patients with LVNC. Sign of Anttonen 140 ms (point J – top of the T wave, normal value above 150 ms)[42].

segments affected by noncompaction and found that 95% did not originate from LVNC areas, and 10% had a true myocardial origin. The rest originated in other structures (outflow tracts, fascicles, and mitral and tricuspid annulus). Identifying the basic electrophysiological mechanism of arrhythmogenesis is of interest to select the therapy for these patients (antiarrhythmic drugs, PESH, ablation)[37].

A high prevalence of early repolarization has been reported in patients with LVNC, especially in those with malignant ventricular arrhythmias (75%) compared to 31% in cases without them. It is known that this finding is associated with arrhythmias, including ventricular fibrillation and SD events. One possible mechanism is increased trabeculation with deep intramyocardial invagination in the deep Purkinje system of the middle myocardium, resulting in delayed depolarization, inhomogeneous repolarization and transmural heterogeneity. Whether there are genetic factors at the channels level which influence vulnerability to ventricular arrhythmias and early repolarization, or wheter it is a domain of the I_{to} current of the ventricular epicardium remains unknown.

Normal LV twisting is absent in LVNC, possibly due to immaturity of the spiral system. Ventricular tachycardia and fibrillation are frequent, Caliskan *et al.*[38] studied 84 patients with this disease and reported that 39% had early repolarization (6% located in inferior leads, 27% in lateral leads and 15% in both; none were observed in leads V_1-V_3). Cases presenting with ventricular tachycardia-fibrillation had early repolarization in 75% vs. 31% in other patients. Outcome appeared worse in patients with these arrhythmias and early repolarization (which is also seen in idiopathic ventricular fibrillation and short QT syndrome) and is more important when the ST segment is horizontal or descending, and of lower risk if it is fast ascending. One cause of this repolarization may be the greater trabeculation of the LV in deep endomyocardial invaginations and there seems to be a possible association between both. Quinidine, which restores transmural electrical homogeneity, aborts arrhythmic activation, decreases the early repolarization pattern and diminishes or eliminates arrhythmias. In summary, early repolarization contributes to stratify risk in these patients and sometimes helps identify those who need ICD[38].

There are scarce data on ICD devices in patients with LVNC. Prophylactic ICDs are implanted for primary or secondary prevention, with therapies that are usually suitable for both groups. In another investigation, Caliskan *et al.*[39], in another investigation, studied 77 adult patients, 44 with ICD, as indicated in the guidelines for non-ischemic CMPs (ventricular tachycardia and fibrillation, and severe HF). A 19% of patients had nappropriate therapy in primary prevention and 25% in secondary prevention. A 13% presented with appropriate therapy in primary prevention and 33% in secondary. Ventricular tachycardia is reported in 38-47% of LVNC patients and SD in 13-18% (including ventricular tachycardia and fibrillation). Histological examination confirms myocardium around deep intratrabecular recesses that may create slow conducting zones with possible reentries. Impaired flow reserve (intermittent ischemia) may contribute to this arrhythmogenesis. These authors consider inducibility of sustained ventricular tachycardia by PESH to have a little value for risk stratification in these patients and suggest that premature ventricular contractions do not seem to be associated with a worse prognosis although data are limited[39].

There are few reports on the possible benefits of ablation in patients with LVNC and ventricular arrhythmias. Muser *et al.*[40] studied 9 patients, 3 with ventricular tachycardia and 6 with extrasystoles (in these, non-compact medioapical zones versus arrhythmias that originate in basal regions of the LV or in the papillary muscles, or both), the noncompaction process was extended to the segments of the papillary muscles; in the remote areas to the noncompact myocardium, the pathological muscle showed fibrosis, disruption of the cellular architecture and non-compact myocytes. This is the first series of ablation in ventricular arrhythmias refractory to other treatments in the LVNC, and good results are reported (89% of the cases and improvement of the ejection fraction in 50%) with few complications. Abnormal cell-to-cell coupling in noncompacted myocardium, regional microvascular dysfunction, and abnormal activity of ion channels are ideal for reentries and focal mechanisms. The origin of ventricular arrhythmias is related to the non-compacted ventricle, especially in ventricular tachycardia. Substrate distribution is unusual and involves the ventricular outflow tract, LV apex and mid-apical area.

In the figures (**Fig. 2**, **Fig. 3** and **Fig. 4**) several examples of LVNC with different electrocardiographic alterations and arrhythmias are presented.

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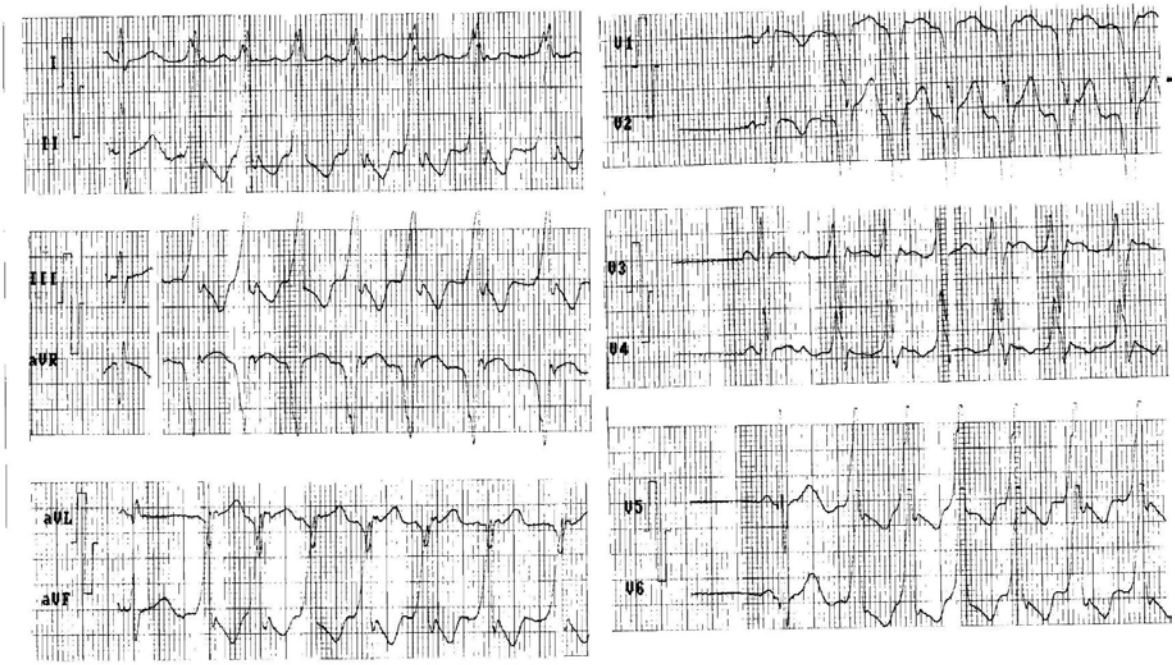

Figure 4. A 23-year-old woman with probable left ventricular non-compaction who meets the Stollberger criteria and partially the Jenni criteria[28,43]. Wide-QRS complex tachycardia, with left bundle branch block morphology, dissociated, incessant, originating from the right ventricular outflow tract. A first sinus complex is observed, followed by continuous bouts of tachycardia.

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