JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 66, NO. 5, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.06.017

REVIEW TOPIC OF THE WEEK

Isolated Noncompaction of the Left Ventricle in Adults

Ayman Hussein, MD,* Ahmadreza Karimianpour, DO,† Patrick Collier, MD, PhD,* Richard A. Krasuski, MD*‡

ABSTRACT

Isolated left ventricular noncompaction (ILVNC) is a cardiomyopathy that was first described in 1926 as a "spongy myocardium." The disorder results from intrauterine arrest of compaction of the loose interwoven meshwork of the fetal myocardial primordium and subsequent persistence of deep trabecular recesses in the myocardial wall. The classical clinical presentation is a triad of heart failure, arrhythmias, and embolic events from mural thrombi. ILVNC has been associated with several autosomal dominant, X-linked, and mitochondrial genetic mutations that are also shared among other cardiomyopathies. Over the past decade, ILVNC has been subject to intensive research, as it increases the risk for sudden cardiac death. This review focuses on the current understanding of ILVNC in adult populations and attempts to provide organized insight into the disease process, screening, diagnosis, management, role of device therapy, and prognosis. (J Am Coll Cardiol 2015;66:578–85) © 2015 by the American College of Cardiology Foundation.

Isolated left ventricular noncompaction (ILVNC) is a rare cardiomyopathy classified as a primary genetic cardiomyopathy by the American Heart Association (1). It is still considered unclassified in the European Society of Cardiology classification (2), as it remains unclear whether it represents a distinct disease process or a morphological trait shared by many phenotypically different cardiomyopathies.

ILVNC results from intrauterine arrest of compaction of the loose meshwork of the fetal myocardial primordium (3,4) and subsequent persistence of deep trabecular recesses in the myocardial wall. The first pathological description of spongy myocardium dates back to 1926 (5). However, ILVNC was first designated as a clinical entity in 1984, identified by the isolated persistence of "sinusoids" in the left ventricle (6), which communicate with the left ventricular cavity and are usually filled with blood from the ventricle. Note that if noncompaction is concomitantly present with other structural abnormalities (i.e., hypertrophic cardiomyopathy), the diagnosis of "left ventricular noncompaction in association with" is more appropriate (7).

ILVNC has gained increasing attention (1,2) because of its association with high rates of mortality and morbidity in adults, including heart failure, thromboembolic events, and tachyarrhythmias (8). Paradoxically, its prognosis appears better when identified early in childhood (9). This review focuses on the current understanding of ILVNC in the adult population and provides an illustrative portrayal of the disorder.

EMBRYOLOGY

During embryogenesis, the myocardium consists of a loose network of interwoven fibers separated by deep intertrabecular recesses linking the myocardium with the left ventricular cavity. Between the fifth and eighth weeks of embryonic development, this meshwork compacts, proceeding from the epicardium to the endocardium and from the base of the heart to the apex (3,10–12). Ventricular noncompaction results

From the *Department of Cardiovascular Medicine, Cleveland Clinic Foundation, Cleveland, Ohio; †Department of Internal Medicine, Cleveland Clinic Foundation, Cleveland, Ohio; and the ‡Sydell and Arnold Miller Family Heart & Vascular Institute, Cleveland Clinic Foundation, Cleveland, Ohio. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

Manuscript received March 12, 2015; revised manuscript received June 9, 2015, accepted June 10, 2015.

from intrauterine arrest of this process, due to pressure overload or myocardial ischemia preventing the normal compaction process and regression of the myocardial sinusoids (8).

Although noncompaction of the myocardium is seen in association with other congenital cardiac abnormalities (**Table 1**), it can also occur as a primary disorder in the absence of other structural heart disease (7). This latter circumstance, referred to as ILVNC, is the topic of this review.

PREVALENCE

The true prevalence of ILVNC is difficult to determine because diagnostic criteria are not standardized. Most studies addressing this issue are from tertiary medical centers and performed in populations with symptoms or abnormal physical examination findings and for family screening of patients with the disorder (8,9,13–15). Therefore, a major limitation is that available prevalence data are derived from retrospective databases fraught with selection biases. In a report from Switzerland, only 0.014% of patients undergoing echocardiography between January 1984 and December 1998 were identified as ILVNC cases (8). However, in the past decade, increased awareness of the disorder, as well as improvements in echocardiographic image acquisition and processing, have led to greater detection. Thus, the Swiss study is likely to have underestimated disease prevalence. ILVNC is significantly more prevalent within the heart failure population (16,17), which is not surprising, as heart failure remains its most classical presentation.

GENETICS

ILVNC is a genetically heterogeneous disease that can be either familial or sporadic. Familial recurrence appears more commonly in adults with ILVNC (18) than in children (19) and may be autosomal dominant, X-linked, or mitochondrial in origin. The recurrence of noncompaction phenotypes in families varies between 18% and 50% (8,20,21). Although retrospective designs limit their general applicability, prior studies suggest that a detailed pedigree analysis of patients presenting with ILVNC is warranted. It is also generally recommended that asymptomatic relatives of affected individuals be screened using echocardiography (22).

Table 1 describes the major gene mutations associated with LVNC that overlap with other cardiac disorders. Notably, mutations in the sarcomeric cardiac beta-myosin heavy chain gene (MYH7), previously linked with hypertrophic cardiomyopathy, restrictive cardiomyopathy, and dilated cardiomyopathy, have been identified in 2 families with ILVNC (23), suggesting potential overlap among cardiomyopathy genes (23–35).

Despite the major advances noted earlier, the precise correlation between genotype and phenotypic expression in cardiomyopathies is poorly understood. Available data suggest that, for certain mutations, noncompaction and hypertrophic, restrictive, and dilated cardiomyopathies are not clearly distinct entities (26,27). In summary, the currently available genetic data suggest significant genetic heterogeneity in ILVNC, and the major genetic cause for familial

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

ICD = implantable cardioverter-defibrillator

ILVNC = isolated left ventricular noncompaction

NYHA = New York Heart Association

TABLE 1 Major Gene Mutations Associated With LVNC and Their Overlap With Other Cardiac Disorders

Disorder	TAZ-G4.5 Mutation	DTNA Mutation	Z-Band Mutation	FKBP12 Mutation	LMNA Mutations	NKX2.5, TBX5, CSX Mutations	ACTC, TNNT2, MYH7 Mutation	SCN5A Mutation	HCN4 Mutation
LVNC	×	×	×	×	×	×	×	×	×
Ventricular/atrial septal defect		×		×		×			
Arrhythmogenic right ventricular cardiomyopathy				×					
Dilated cardiomyopathy	×		×	×	×		×		
Hypertrophic cardiomyopathy							×		
Other cardiomyopathies*	×		×			×		×	
Other conduction abnormalities†					×	×	×	×	×
Tetralogy of Fallot						×			
Ebstein anomaly						×			
Brugada syndrome								×	
Romano-Ward syndrome								×	

*X-linked infantile cardiomyopathy, X-linked endocardial fibroelastosis, hypoplastic left heart syndrome. †Bundle blocks, atrioventricular nodal blocks, tachyarrhythmias, bradyarrhythmias.

ACTC = alpha-cardiac actin (24); CSX = cardiac specific gene located on 5q (65,66); DTNA = alpha-dystrobrevin gene, transition C to T mutation, located on 18q12 (19); FKBP12 = responsible for release of calcium from sarcoplasmic reticulum via ryanodine receptor (67); HCN4 = hyperpolarization-activated cyclic nucleotide channel 4 (68); LMNA = lamin A/C related sequence located on 1q22 (69); LVNC = left ventricular noncompaction; MYH7 = B-myosin heavy chain (23–25); NKX2.5 = homeobox protein located on chromosome 5 (65,66); SCN5A = human cardiac sodium channel alpha-subunit gene (70); TAZ-G4.5 = encodes tafazzin located on Xq28, (18,19,71); TBX5 = T-box transcription factor located on chromosome 12 (65,66); TNNT2 = cardiac troponin T (24); ZASP = Z-band alternatively spliced PDZ motif-containing protein on 10q22.2-q23.3 (72).