Left Ventricular Noncompaction Diagnosis and Management Relevant to Pre-participation Screening of Athletes

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Left ventricular noncompaction (LVNC) has been extensively studied over the last years, and an increasing number of cases have been reported worldwide, with a large proportion comprising young and asymptomatic subjects, including athletes. The current epidemic of LVNC is likely the consequence of several causes, that is, the increased awareness of the disease and the refined cardiovascular imaging techniques. The current diagnostic methods, based uniquely on definition of morphologic findings, do not always resolve the overlap of a physiological myocardial architecture comprising a prominent trabecular pattern from a mild phenotypic expression of the real disease. Appropriate criteria for identification and management of LVNC in athletes have, therefore, become a novel challenge for cardiologists and sport physicians, who are required to solve the question of diagnosis and appropriate management in the setting of pre-participation cardiovascular screening. Indeed, although it is important to timely identify a true myocardial disease, to reduce the burden of adverse cardiac event in a young athlete, in contrast, a misdiagnosis of LVNC may lead to unwarranted restriction of the athlete lifestyle, with detrimental psychological, social, and economic consequences. This review report has been planned, therefore, to help physicians in diagnosing and managing athletes presenting with a morphologic pattern suggestive of LVNC with specific focus on criteria for advising sport participation. **(Am J Cardiol 2015;116:801−808)**

Left ventricular noncompaction (LVNC) is a myocardial disorder phenotypically characterized by increased trabeculation of left ventricular (LV) chamber, typically 2-layered myocardium with a thin subepicardial compacted layer and a noncompacted thicker hypertrabeculated layer.[1−4] Phenotypically, LVNC may present with various degrees of LV dilation and dysfunction.[4,5] Recent observations suggest a larger prevalence of the disease than previously described; Paterick and Tajik[5] reported that cases identified by echocardiographic examinations grew from 0.4% in 2010 to 1.0% in 2013. Greutmann et al[6] reported similar experience, with a progressively increasing number of new diagnoses from 1984 to 2006 in a tertiary care referral center. The newly diagnosed cases comprise an increasing proportion of asymptomatic subjects, including athletes, with a mild phenotypic expression of the disease. Recently, Gati et al[7] reported the occurrence of hypertrabeculation (defined as at least 3 trabeculations of at least 3 mm) in 18.3% of 1,146 athletes, with a subset of 8.1% athletes fulfilling the conventional echocardiographic criteria for LVNC. The increased trabecular pattern incidentally observed in an otherwise normal heart should not be considered sufficient for diagnosis of LVNC. Appropriate criteria for identification and management of LVNC in athletes have, therefore, become a novel challenge for cardiologists and sport physicians, who are required to solve this question in the setting of pre-participation cardiovascular (CV) screening.

Classification and Epidemiology

The World Health Organization and the European Society of Cardiology initially described LVNC as an unclassified cardiomyopathy.[8,9] In contrast, the American Heart Association classified LVNC as a primary genetic cardiomyopathy.[10] Inconsistency in the LVNC classification was related to uncertainty regarding the true nature of the disease, that is, whether it represents a primary cardiomyopathy or a phenotypic variant of other cardiomyopathies. LVNC may occur as a part of syndromes like Barth syndrome, myotonic dystrophy, mitochondrial myopathies, and zaspopathies, in association with congenital heart disease, or in neuromuscular disorders.[11−15] LVNC has been identified in families with hypertrophic cardiomyopathy (HCM) or dilated cardiomyopathy (DCM), and recent genetic advances have demonstrated a common genetic pathway related to abnormal sarcomeric proteins, supporting the hypothesis that LVNC may be a phenotypic variant of other cardiomyopathies.[16−18] A specific genetic background, however, and familiar occurrence have been identified in many cases of LVNC, suggesting that it may be considered as a primary myocardial disease.[19−21] A recent classification of the myocardial diseases, named MOGE,

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Table 1
Incidence of sudden cardiac death and sustained ventricular tachycardia in major left ventricular noncompaction studies

Author	Year	Sample size (n)	Age (years)	Gender (male)	Mean Follow-up (months)	Incidence of SCD*	Incidence of Sustained VT†
Oechslin [28]	2000	34	42±17	74%	44	18%	9%
Murphy [16]	2005	45	37±17	62%	46	2%	0%
Aras [45]	2006	67	41±18	66%	30	9%	2%
Stollberger [46]	2007	86	52±16	76%	51	4%	-
Lofiego [27]	2007	65	45±16	37%	46	5%	6%
Habib [26]	2011	105	45±17	66%	28	0.1%	6%
Greutman [6]	2012	132	41±17	35%	32	9%	4%

* Sudden Cardiac Death.
† Ventricular Tachycardia.

proposed by Arbustini et al,[22] is based on 5 characteristics of cardiomyopathies, that is, morphofunctional features (M), organ involvement (O), genetic inheritance (G), etiology (E), and heart failure stage (S). In the context of morpho-function characteristics, the LVNC pattern has been described as a distinct phenotype that may be present either in isolation or associated with DCM or HCM.

Prevalence of LVNC in the adult population ranges from 0.014% to 1.3%.[23] Incidence of the disease in infants and children has been reported as 0.81 and 0.12 cases per 100,000 per year, respectively, representing ~9% of all cardiomyopathies in childhood.[24,25] Gender prevalence is heterogeneous in studies, and there is not a clear predominance gender related[16,26–28]; data on ethnic differences are scarce, but few studies seem to suggest increased prevalence in black subjects.[7,29]

Pathogenesis: At the end of the fourth week of the gestational age, rich trabeculations develop from the endocardial layer with a centripetal growth. The trabeculations are aimed to increase the endocardial surface area, enabling efficient myocardial perfusion in the absence of coronary arteries. At the end of the eighth gestational week, parallel to the development of the coronary circulation, the trabecular pattern becomes compacted starting from the basal segments toward the apex and increasing the thickness of the epicardial layer. Some of the trabeculae coalesce to produce the papillary muscles, whereas the intertrabecular recesses collapse to form the capillary circulation.[30] An arrest in the compaction process could explain persistent myocardial trabeculations and the double-layered appearance of the myocardial wall.[20,21,31,32] This hypothesis explains why LVNC may be identified in fetuses and present at birth. However, identification of this condition in adult patients has raised the question whether an acquired phenotype of the disease may exist.[31] In this regard, an interesting hypothesis is that the observed myocardial changes may represent the combined effect of genetic and environmental factors. Changes in sarcomere proteins may be genetically determined but might lead to morphologic LV changes only later in life, in a way similar to what occasionally occurs in HCM or DCM.[20,33] Additionally, trabeculations have been observed in subjects with hypertensive heart disease, congenital heart disease, heart failure, sickle cell anemia, athletes, and pregnant women, all conditions characterized by an increased pressure or volume load.[7,12,13,34–36] Therefore, it has been hypothesized that increased trabeculation in these conditions may represent an adaptation of the myocardial architecture to increased load conditions.[31,36,37] This hypothesis may justify the increased prevalence of trabeculation described in trained athletes.[7] An additional support comes from a recent study, where the morphologic cardiac changes occurring during the pregnancy (i.e., a physiological model of chronic increased preload) were evaluated; of note, 25% of 102 women developed increased trabeculations during pregnancy, with 8% fulfilling criteria for LVNC.[36] Interestingly, the vast majority of women showed a complete regression of trabeculation in the post-partum period. Finally, D'Ascenzi et al[38] recently reported longitudinal data on training-induced hypertrabeculation in basketball players. Compared with pre-training, athletes developed an increased trabecular pattern at peak of training, associated with electrocardiographic (ECG) repolarization changes that were more prominent in Afro-Caribbean athletes.

Genetics: Several studies investigated the genetic background of LVNC. A pathogenic mutation has been identified in up to 41% of the affected subjects, and a familial occurrence has been described in up to 64% of the probands.[19] However, the prevalence of genetic mutations is difficult to assess, in that only selected candidate genes have been assessed (instead of whole-genomic sequencing), and usually only probands with more striking phenotypic changes have, so far, been tested for DNA anomalies.[31] In adult patients, the autosomal dominant inheritance with incomplete penetrance is the usual technique of disease transmission.[20,39,40] Hoedemaekers et al[19] identified 11 genes mutations, with 6 of them related to sarcomere proteins (*MYH7, MYBPC3, TNNT2, ACTC, TPM1*, and *TNNI3*), 2 to calcium-handling proteins (*PLN* and *CASQ2*), and the remaining 3 to *LMNA, LDB3*, and *TAZ* genes. Specifically, mutation in myosin heavy chain (*MYH7*) represents the most frequent defect, observed in 17% of mutation carriers.

Sarcomeric protein mutations have been reported in a significant proportion of patients with LVNC (29%).[21] In detail, mutations in 5 sarcomeric proteins were described, including *MYH7* in most cases, followed by *MYBPC3*, *ACTC1, TNNT2*, and *TPM1*.[20,21] Finally, 2 recent studies describe an association between the LVNC phenotype and mitral valve prolapse and bradycardia, with causative mutation in the *HCN4* gene.[41,42] These observations substantiate the concept that LVNC is a genetically