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Editorial

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Left Ventricular Noncompaction in Association with Congenital Heart Disease

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Abbreviations: CHD: Congenital Heart Disease; LVNC: Left Ventricular Noncompaction; AHA: American Heart Association; ESC: European Society of Cardiology; ANF: Atrial Natriuretic Factor; EF: Ejection Fraction

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Introduction

Left ventricular noncompaction (LVNC) is a heterogeneous structural myocardial abnormality of unknown aetiology characterised by multiple prominent ventricular trabeculations, deep intertrabecular recesses, and a bi-layered myocardium consisting of a thick, spongy, non-compacted endocardial layer and a thin, compacted, epicardial layer [1]. Abnormal trabeculations are typically most evident in the apical portion of the left ventricle with extension to the lateral left ventricular wall, distal to the papillary muscles [1,2]. The left ventricular cavity communicates with the intertrabecular spaces without evidence of perfusion by the epicardial coronary artery system [2]. According to the American Heart Association (AHA) LVNC is classified as a distinct cardiomyopathy since 2006, but it is still considered an unclassified cardiomyopathy by the European Society of Cardiology (ESC) [3,4].

In the early embryo (Carnegie stage 13 of human development), the larger part of the developing cavities of both ventricles is occupied by a spongy network of fine trabeculations, with little difference noted in coarseness between the right and left ventricle [5,6]. It has been speculated that arrest of endomyocardial morphogenesis with failure in the compaction pathway represents the pathogenetic mechanism underlying LVNC, however this hypothesis is unproven [2,3]. By Carnegie stage 18, the walls of both ventricles have thickened significantly, a process attributed to proliferation and remodeling [5,6]. Thickening of the ventricular myocardium necessitates the formation of the coronary vasculature, with the endothelial and smooth muscle cells deriving from epicardially derived cells. The newly formed vascular network supplies blood to the muscle of the ventricle, once blood can no longer be obtained via diffusion. The embryonically formed trabeculations therefore constitute a progressively smaller part of the ventricular myocardial mass during fetal development [7]. Thus, it seems likely that noncompaction of the ventricular myocardium results from abnormal persistence of the trabecular layer rather than from non-compaction of the ventricular wall [6]. If persistence of the embryonic sinusoids were the pathogenetic mechanism of LVNC, direct communication with the coronary arteries would be expected and should have been documented; however, this contradicts the definition of LVNC [1,2]. Also, as the excessive trabeculations in LVNC do not have the embryonic identity (have very few Purkinje cells,

are atrial natriuretic factor (ANF) negative and are abundant in coronary vasculature) and therefore non-compaction cannot be considered a retention of the embryonic design, the lesion may alternatively result from the compact wall growing into the ventricular lumen in a trabecular fashion [7].

Left ventricular noncompaction has been identified at all ages, even in utero and its clinical presentation is highly variable [1,2,8]. Patients can be totally asymptomatic or present with signs and symptoms of heart failure. Conduction disturbances occur frequently in LVNC, as well as supraventricular and ventricular arrhythmias, many of which are life threatening and can lead to sudden cardiac death. The endomyocardial morphology of LVNC is a predisposing factor for the development of mural thrombi within the sinusoids [1,2]. Thrombi can also originate from the ventricular cavity in cases of severe systolic dysfunction, or from the atrium in patients with atrial fibrillation [1]. Cardioembolism can manifest as stroke or transient ischaemic attack, mesenteric, myocardial or renal infarction, and peripheral embolism [1].

Left ventricular noncompaction is diagnosed more frequently in recent years, probably due to increased awareness of the condition, advances in diagnostic imaging, and systematic screening of first degree relatives of patients with LVNC and of those with neuromuscular disorders [1]. Diagnosis of LVNC is based on non-invasive imaging, usually transthoracic echocardiography because of its widespread availability, lack of radiation exposure and low cost and to a lesser extent on cardiac magnetic resonance imaging [9,10].

Three diagnostic algorithms using echocardiographic criteria have been proposed, all of which require the presence of a two-layered myocardium for the diagnosis of LVNC [1]. Agreement between existing echocardiographic diagnostic proposals however, is poor and thus the diagnostic criteria for LVNC are controversial [9]. According to Chin., *et al.* an X/Y ratio < 0.5 is required for diagnosis (X: the distance between epicardial surface and trough of the intertrabecular recesses and Y: the distance between epicardial surface and peak of the trabeculations) [11].

According to Jenni., *et al.* ("*Swiss criteria*") a NC/C ratio in end-systole > 2.0 (NC: non-compacted layer thickness and C: compacted layer thickness), absence of other cardiac abnormality and intertrabecular perfusion from the ventricular side are all requisites for echocardiographic diagnosis [12]. The latter, as well as the presence of more than three trabeculations are considered essential diagnostic criteria, as suggested by Stöllberger., *et al.* ("*Vienna criteria*") [13].

Left ventricular noncompaction can be further classified as con¬genital or acquired, or as paediatric versus adult. In addition, LVNC can be categorized as symptomatic or asymptomatic and may be present with or without a neuromuscular disorder [1]. At least eight different phenotypes of LVNC seem to exist, all of which have different outcomes [2,14]. Although, LVNC was originally described as an isolated cardiomyopathy without other structural cardiac abnormalities, it is commonly associated with other forms of cardiomyopathy or congenital heart disease (CHD) [1,2]. The reason for the variability in categorization is the fact that the pathogenesis of LVNC remains unclear, the diagnostic criteria are controversial, and the clinical implications of the disorder, as well as the optimal management of patients are under debate [2].

"Congenital heart disease form" of Left ventricular noncompaction

As previously stated, LVNC was originally described as an isolated cardiomyopathy without other structural cardiac abnormalities [1,2]. However, LVNC has been subsequently described in all age groups in association with most forms of CHD. Right-sided lesions, especially Ebstein's anomaly, pulmonic stenosis, pulmonary atresia, tricuspid atresia, and tetralogy of Fallot with or without double outlet right ventricle are more frequently coupled with LVNC. However, septal defects (ventricular septal defect and/or atrial septal defect), hypoplastic left heart syndrome and other left-sided lesions have also been reported in association with LVNC [2].

The CHD form of noncompaction has been associated with mutations in distinct genes, although a causal relationship between these monogenic disorders and LVNC remains to be established [1]. Genetic abnormalities may cause both structural congenital malformations and impair left ventricular myocardial differentiation. Alternatively, haemodynamic disturbances during fetal life or even

postnatally, such as pressure overload may trigger or contribute to alterations of left ventricular architecture in genetically susceptible individuals [1,14].

The co-existence of CHD and LVNC is predominantly observed in children [15,16]. Septal defects, a patent arterial duct, and Ebstein's anomaly are the most prevalent malformations [15,17]. The efficacy of surgical treatment of these patients is largely unknown; however there is no doubt that operative repair of congenital cardiac malformations in LVNC carries a higher risk [16]. Outcomes depend on the specific CHD, but may be worse than the postoperative outcome of the same CHD without LVNC. In this case, the surgeon, cardiac anaesthesiologist, and cardiac intensivist must pay close attention to pre-existing deficiency in myocardial function and manage the patient accordingly [18].

Children who present with heart failure and poor ventricular function (ejection fraction, EF < 50%) have worse outcome (death or intractable heart failure) postoperatively [16]. In these subjects, poor ventricular function may be attributed to LVNC, CHD or the combined effects of both. Careful evaluation to select appropriate therapy may result in lower mortality rates. Indeed, surgery can be effective in relieving heart failure (as assessed by NYHA functional class), improving ventricular function, and decreasing heart size [16].

Left ventricular noncompaction was detected in 2% of children with CHD undergoing left ventricular angiography in a single tertiary referral, in Melbourne, Australia between 1994 and 2000, with a prevalence varying from 1% of children with a balanced ventricular arrangement, to 22% of those having a functionally single left ventricle. The authors speculate that the particularly high prevalence in children with functionally single left ventricle may be due to abnormal pressure or volume loading beginning in fetal life, or a common genetic factor resulting in both the functionally univentricular arrangement and ventricular noncompaction [19].

The rate of death of patients with evidence of noncompaction was double that of those with comparable cardiac structural abnormalities without noncompaction. The presence of noncompaction and a functionally single left ventricle were each associated with a doubling of mortality, the effect being cumulative. Moreover, nearly one-fifth of surviving subjects with LVNC developed persisting cardiac dysfunction, which sometimes became manifest many years after their initial presentation [19]. Microcirculatory coronary dysfunction has been described in subjects with isolated LVNC [20]. This may result in ventricular dysfunction and cardiac arrhythmias, and may account for the late impairment of myocardial performance in the children included in this study [19]. Ventricular noncompaction might also explain the increased incidence of late myocardial dysfunction among children with functionally single ventricles. It should be noted that the outcomes of subjects reported in this relatively old and retrospective study should be interpreted cautiously. They are probably not truly representative of all children with these conditions in the current era, as symptomatic patients and those with more complex cardiac anatomy, are more likely to undergo cardiac catheterization.

Appropriate therapeutic approach may include pharmacologic therapy with diuretics for volume overload, complex pharmacologic therapy for patients with restrictive physiology or pulmonary hypertension, anticoagulation for cardioembolism and invasive therapy with catheter interventions or surgical repair, depending on the associated lesions. In addition, cardiac rhythm disturbances need to be identified and antiarrhythmic medications, pacemakers, implantable defibrillators or radiofrequency ablation interventions should be considered [14,16,18].

In case series of children diagnosed with LVNC, the prognosis appears to be poorer compared to adults with some investigators finding higher mortality in individuals with low EF. It is likely that those with more severe forms of excessive trabeculations present earlier in life, perhaps explaining the more benign adult forms [21]. In adults the most common congenital cardiac defects associated with LVNC are various forms of left ventricular outflow tract abnormalities and obstructions, Ebstein's anomaly and tetralogy of Fallot. The prevalence of LVNC is highest for Ebstein's anomaly followed by aortic coarctation, tetralogy of Fallot, and bicuspid aortic valve [14]. The number of affected patients within adult series is relatively small. Thus, to determine the impact of the additional presence of LVNC on cardiovascular outcomes in adult patients with CHD, larger cohorts with long-term follow-up are needed.

Conclusion

Currently, the pathogenesis of LVNC remains unclear, the echocardiographic diagnostic criteria are controversial, and the clinical implications of the disorder, as well as the optimal management of the patients are under debate. Right-sided lesions, especially Ebstein's anomaly, pulmonic stenosis, pulmonary atresia, tricuspid atresia, and double outlet right ventricle are more frequently coupled with LVNC. Septal defects, hypoplastic left heart syndrome and other left-sided lesions have also been reported in association with LVNC with differences in the more prevalent forms of CHD between paediatric and adult studies. The CHD form of noncompaction has also been associated with mutations in distinct genes, although a causal relationship between these monogenic disorders and LVNC remains to be established. Meticulous follow-up of these patients by specialised medical teams may provide a better understanding of the interaction between genetic and haemodynamic factors that define the phenotypic spectrum of LVNC and guide medical, interventional and surgical management in the setting of CHD.

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