Diagnosis of Left Ventricular Non-Compaction Cardiomyopathy facilitated by the use of 3D Echocardiography a case-report.

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Keywords: Left Ventricular Non-Compaction Cardiomyopathy, 2D Echocardiography, 3D Echocardiography, LVNC criteria.

Abstract

Left Ventricular Non-Compaction Cardiomyopathy is a distinct and rare cardiomyopathy characterized by prominent trabeculae and deep intertrabecular recesses. The condition has a prevalence of 0.014-1.3% in the general population. Clinical Manifestations of the disease include dyspnoea, chest pain, palpitations, and heart failure. Early diagnosis of the disease has been proven to be challenging among physicians due to paediatric patients being asymptomatic. In this paper we present the diagnosis of our paediatric patient which was assisted with
a three-dimensional echocardiogram, and we review the gaps in the current diagnostic criteria. The aim of this paper is to propose the incorporation of 3D echocardiography in diagnostic criteria of the disease and refer to the importance of this examination in early diagnosis.

Introduction

Left Ventricular Non-Compaction Cardiomyopathy (LVNC) is a distinct phenotype, that can be either sporadic or familial and is characterized by prominent trabeculae and deep intertrabecular recesses resulting in 2 layers of compacted and non-compacted myocardium that communicate with the left ventricular cavity. It's prevalence in the general population is approximately 0.014 to 1.3[1,2]. The pathogenesis of LVNC was found to be correlated with failure in the development of the fetal myocardium primordium resulting in a loose interwoven meshwork and an abnormal trabecular layer in the ventricular wall[3]. Prominent trabeculations as seen in LVNC may develop during adult life due to remodeling in response to LV loading as seen in some athletes and some

individuals, who are hypertensive, pregnant, or diagnosed heart failure[4].

Although LVNC can induce several manifestations, presentation of the disease is nonspecific, and a diagnosis should be considered with or without symptomatology. LVNC signs and symptoms include dyspnoea, chest pain, palpitations, syncope or presyncope, cardioembolic stroke and heart failure[5]. Paediatric patients are usually asymptomatic and lack severe manifestations, while at the same time not many sets of criteria have been used in the aforementioned age group, making the diagnosis more challenging[6]. On the contrary, complications of the disease have been greatly reported in many studies and includeheart failure with reduced ejection fraction,thromboembolic and cerebrovascular events, hypertension and arrythmias e.g., ventricular and atrial arrhythmias such as non-sustained and sustained ventricular tachycardia, atrial fibrillation[7].

The gold standard in the diagnosis of LVNC is the use of two-dimensional transthoracic echocardiography(2DTTE) which aids in the identification of pathoanatomical characteristics[8]. For the diagnosis of LVNC using 2DTTE there are established criteria which have been extensively referred to in literature. Jenni et al. (2001) proposed diagnostic criteria for LVNC based on the end systolic ratio of the noncompacted to compacted myocardium of >2:1 with the use of 2DTTE. Furthermore, the Jenni et al. criteria also include: no other coexisting cardiac abnormalities, a two-layer structure with a compacted thin epicardial band and a much thicker non-compacted endocardial layer of trabecular meshwork with deep endomyocardial spaces, the predominant localization of the pathology to mid-lateral, apical and mid-inferior areas and finally, colour doppler evidence of deep perfused intertrabecular recesses[9].

Although Jenni et al. criteria are well known and commonly used in 2DTTE diagnosis of LVNC other criteria that have been proposed are the Chin et al. and the Stöllberger et al.. Chin et al. diagnostic criteria include a decreased X/Y ratio from the base to the apex of the myocardium as well as absence specific cut-off. The above criteria have been highly recognised in the diagnosis of LVNC and can be used with high accuracy in ages 11 months to 22 years of age. Furthermore, Stöllberger et al. criteria include the presence of more than 3 trabeculations, trabeculation movement synchronous with the myocardium, trabeculation that are part of the non-

compacted layer of the two layered myocardium and finally, the perfusion of intertrabecular spaces demonstrated by colour doppler. The above criteria have not been widely used in the literature ,however, they can be used in the diagnosis of patients 18 to 87 years of age.

Furthermore, a study conducted in LVNC patients by Caselli et al. proposed a criterion which included a measurement called Trabeculated Left Ventricular Volume (TLV) and its normalized value called %TLV. TLV is measured by finding the left ventricular volume at the bottom of the recesses and subtracting the left ventricular volume at the peak of the trabeculae. The %TLV is then normalized by the measured left ventricular volume at the bottom of the recesses which is then multiplied by 100. Both of the measurements based on the results of the study were found to be much higher in patients with LVNC (TLV > 15.8ml and %TLV > 12.8%) compared to controls and athletes (measurements bellow the LVNC cut-off values). The study found that the measurements were highly reproducible and had a high intraclass correlation coefficient making them a potential candidate for the formation of new criteria of LVNC diagnosis in the future[10].

Due to the low prevalence of the disease, diagnosis of the condition has been shown to be challenging. Subsequently, in the diagnosis of LVNC there are some other diagnostic modalities that can be used in the aiding of diagnosis and visualization of the degree of involvement of the myocardium. Those include of Real-Time 3D Echocardiography (RT3DE), Cardiac Magnetic Resonance (CMR) and genetic screening. In a systematic review conducted, the prevalence of LVNC according to different diagnostic modalities such CMRand 2DTTE was found to be higher in patients undergoing CMR[11] depicting the superiority of the modality as many pathognomonic characteristics can be missed with using 2DTTE solely. The results showed an increasing sensitivity and superiority of CMR compared to 2DTTE for the diagnosis of LVNC which was also demonstrated by Thuny et al.[12]. CMRis the modality currently used when the 2DTTE is undetermined; CMR can help in the identification of fibrosis and scarring in the myocardium as well as pathoanatomical features which can be used supplementary in a suspected LVNC patient. Cardiac computed tomography (CT) can be used in cases where the 2DTTEis non-diagnostic and CMR is contraindicated, not available or

has inconclusive findings [13]. Finally, in

the 2018 Heart Failure Association guidelines the recommendation for genetic testing and family screening were limited to patients with underlying symptomatology and presentation of complications [14].

Case Presentation

In this case report we present a case of a 17-year-old asymptomatic malepatient who was referred for a systolic murmurassessment.The main findings of the initial 2DTTE were end systolic ratio of non-compacted to compacted layers >2, involvement of lateral and inferior midventricular and apical areas of the myocardium and finally, direct blood flow from the ventricular area to the deep intertrabecular recesses using doppler. The patient's diagnosis was further facilitated with the use of RT3DE which aided the visualization of the pathoanatomical areas and the blood flow in the trabeculations which will be the focus of this case report.In figures 3 and 4 there is depiction of both 2DTTE and RT3DE side by side with measurements of non-compaction to compaction ratio and non-compacted width respectively. The above are used in the assessment of criteria fulfilled by our patient which are Jenni et al, Chin et al. and Stöllberger et al., as well as several other important measurements for the assessment of LVNC.

Upon initial assessment of the patient in the office, a CMR imaging study was subsequently requested to confirm the diagnosis of LVNC. The findings depicted a higher ratio in the End-Diastolic (ED) views with an average of 4.0 which is above 2.0 established in the Jenni et al. criteria for diagnosis. It is important to acknowledge that the End-Systolic (ES) ratio was found to be 2.2 which is higher than 2, however, in a study conducted comparing the ES and ED criteria for LVNC in the odds of cardiovascular events found that ES above 2.5 (to 33) had a much higher incident of events[15] which was not the case for our patient.

For the assessment of the patient based on the aforementioned criteria used on the diagnosis of LVNC we found the following results which are summarized in Table 1. In this table we depict the results of our patient based on the three established criteria for diagnosis: Jenni et al., Chin et al. and Stöllberger et al.. On the table we included the measurements required of each criterion (Jenni et al. and Chin et al.) which are referred to as index, with the exception of Stöllberger which does not have measurement parameters.

We also included important parameters for the diagnosis and follow-up of the our patient such as: Ejection fraction, CMR criteria fulfilment, Family History, ECG and manifestations at the time of examination. Furthermore, we calculated the TLV and %TLV of our patient based on the instruction of the Caselli et al. study[10] and found the following:

$$TLV = EVV_{bottom\ of\ recesses} - EVV_{peak\ of\ trabeculae} = 139 - 87 = 52ml$$

$$\%TLV = \frac{52}{139} \times 100 = 37.4\%$$

The above measurements were found to correspond with the findings of LVNC patient measurements of the study. The measurement we found also correlate to the 4-fold increase of LVNC patients of the study compared to controls and athletes. The study proposed that measurements of TLV higher than 15.8ml and %TLV higher than 12.8 (mean 24%) correspond to patients with LVNC and thus, can give us great insights into the diagnosis of the patient and potential progression of the disease if follow-up measurements will be taken.

Discussion

Despite the current guidelines into the diagnosis of LVNC using 2DTTE and supplementary CMR we have determined that the use of RT3DE should also be a potential modality for future diagnosis of LVNC. RT3DE is a non-invasive diagnostic modality with varying applications in the visualization of the heart and associated structures. Applications include analysis of the pericardium, visualization of the left and right ventricular cavities as well as great vessels, wall motion, valvular and congenital disease identification as well as traumatic injury evaluation e.g., myocardial contusion[16]. RT3DE uses multiple ultrasound (US) beams for cardiac visualization generating a pyramidal shaped 3D data set which can encompass most of the times the entire left ventricle (LV). The above enables us to create a more systematic and detailed sectioning and cropping of the LV data set ensuring a definite diagnosis of LVNC and ensuring the accuracy of its extent.Furthermore, sequential cropping of raw data in RT3DE using crop boxes enables the differentiation of myocardial trabeculation from LV clots since visible echoluscent areas representing lysis within the clot are highly improbable for trabeculations which appear solid in serial sectioning.

Caselli et al. described in a study the extent of non-compacted myocardium

using a 3D echocardiographic parameter and concluded that due to the high spatial resolution and accuracy in volumetric quantification it allowed accurate measurement of the extent of noncompacted myocardium and identification of LVNC in patients[17].

Upon reviewing the literature and using RT3DE for our patient we decided that the use of this modality has proven to be highly effective both for the diagnosis of LVNC and the visualization of the degree of involvement of the myocardium. RT3DE can also be proven of high importance in the reassessment of patient with LVNC in follow-up appointment to determine the changes in the ratio of non-compacted to compacted myocardium with advanced accuracy[18].

On the other hand, the gold standard of diagnosis of LVNC, which is the 2DTTE modality has been used for many years in the diagnosis of LVNC. The criteria that 2DTTE follows for diagnosis of LVNC are described in previous sections of the case report and are established by Jenni et al. Although, 2DTTE is the primary source of data collection and diagnosis the examined tissue is visualized in a single slice at a point in time which limits the depiction of the recesses inside the noncompacted portions of the LV which can result in misdiagnosis. Additionally, 2DTTE can underestimate the spatial extent of the trabeculations and thus, limiting the differentiation of myocardial trabeculation from LV clots. The authors alsodemonstrated that both LV trabecular mass and the total number of trabeculations in patients with LVNC were again underestimated significantly by 2DTTE compared toRT3DE[19].

Hence, a RT3DE is an important complementary modality for diagnosis of LVNC, however, we have to address that both RT3DE and 2DTTE have not yet being used for evaluation of LVNC quantitatively in medical practice creating gaps for future research. However, both modalities can be used for an accurate assessment of LV trabecular mass and number of trabeculations which can further create an estimate of the disease severity. To conclude, both 2DTTE and RT3DE can be used concurrently with increasing accuracy for the diagnosis LVNC without any indications of superiority of one of them. The criteria which are most commonly used are the Jenni et al. which most of the literaturerefers to. However, other criteria exist for the diagnosis of LVNC which are established based on the patient’s age and types of measurements and include Chin et al. and Stöllberger et al. In a study conducted in the comparison

between the three diagnostic criteria Chin et al. resulted in the highest sensitivity and specificity amongst the three, whereas, Jenni et al. had the lowest reproducibility and diagnostic validity[18].

Furthermore, 2DTTE is a highly reliable modality for diagnosis of LVNC measuring estimates of ventricular mass and anatomic distribution of trabeculation which has been found to be challenging due to the altered geometry of the LV. Accounting for the limitation of 2DTTE, the RT3DE can substitute for more accurate measurement and underestimation of LV trabecular mass by 2DTTE[19]. Thus, RT3DE should be considered as an effective, accurate and useful modality for the diagnosis of LVNC as a substitute in the 2DTTE quantitative assessment.

Conclusion

To conclude, in our case-study we found that RT3DE is a highly valuable modality in the diagnosis of LVNC and should be used supplementary to 2DTTE. RT3DE was found to have equally and sometimes superior measurements and modalities of visualization of trabeculations present in LVNC patients. Trabeculations of the myocardium are the most sensitive and most important characteristic of the disease and should always be examined with doppler in echocardiography. Lastly, doppler use in RT3DE was found to be superior to the use of 2DTTE as flow through trabeculations was visualized with more accuracy.

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Tables and Figures

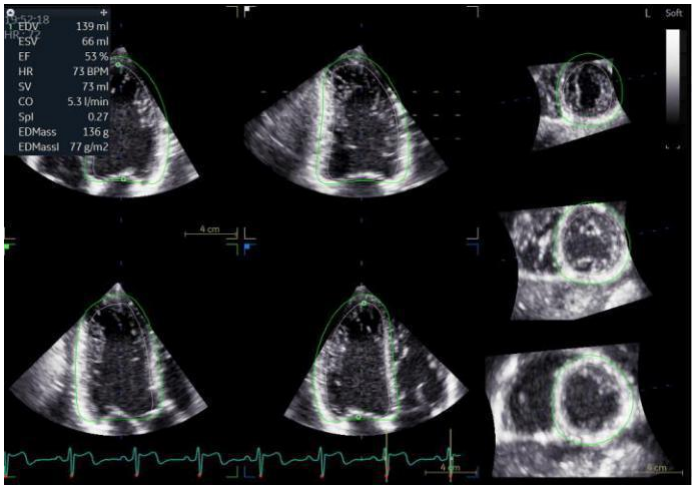


Figure 1: 2D Echocardiography with measured parameters at the bottom of the recesses

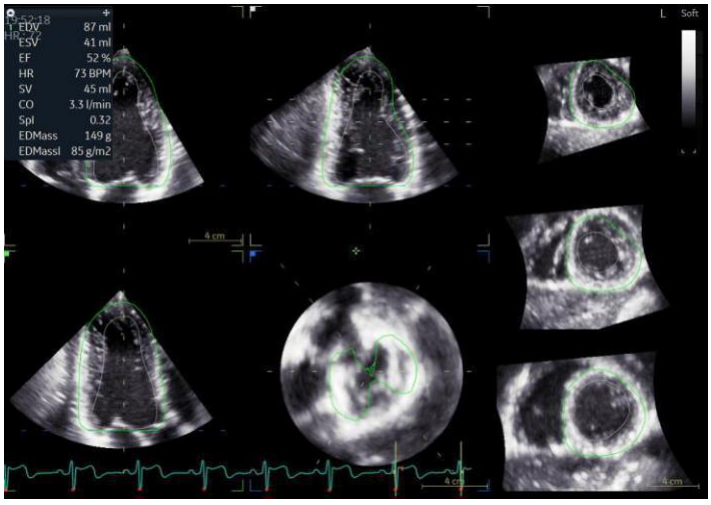
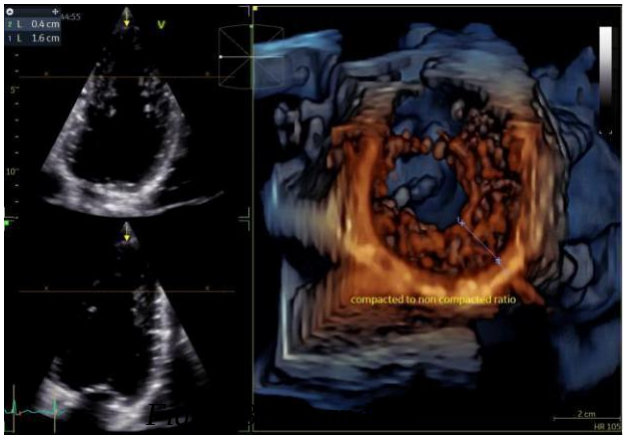


Figure2: 2D Echocardiography with parameters measured at the peak of trabeculae

Table 1: Parameters of assessment of our patient based on international guidelines and criteria proposed for the diagnosis of LVNC

Parameters	*Patient Results*
Jenni et al. Index	4.0
Chin et al. Index	0.25
Stöllberger Criteria	Positive (+)
Ejection Fraction (EF)	53
CMR Criteria	Positive (+) – Noncompacted to Compacted Myocardium Ratio mean value 3.6 (based on four plane views)
Family History (Genetic Testing)	Unknown
ECG Abnormalities	NO
Manifestations (e.g., NMD, CHF, Stroke/TIA)	NO

Abbreviations: CMR: Cardiac Magnetic Resonance, ECG: Electrocardiography, NMD: neuromuscular disorder, CHF: Congestive Heart Failure, TIA: Transient Ischemic Attack.



Echocardiography with measurements on compacted to non-compacted layer ratio

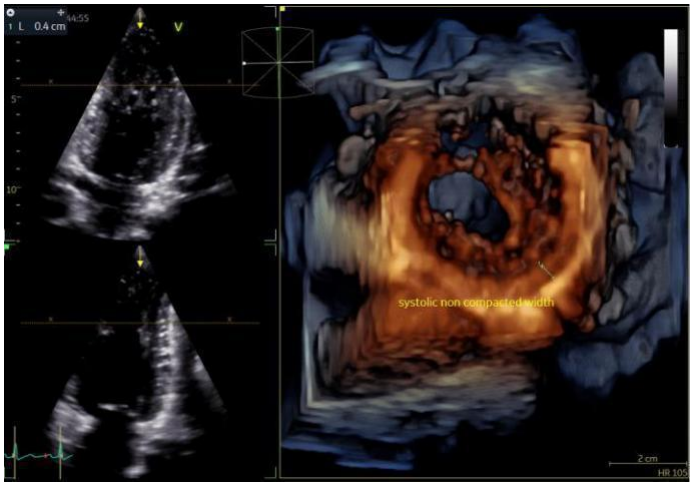


Figure 4: 2D and 3D echocardiography with measurement on the systolic non-compacted width