Case Report

Contrast Echocardiography: Contribution to Diagnosis of Left Ventricular Non-Compaction Cardiomyopathy

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Left ventricular non-compaction (LVNC) is a cardiomyopathy considered to be caused by arrest of normal embryogenesis of the endocardium and myocardium. Echocardiography has been the preferred diagnostic procedure; however, the correct diagnosis is often missed or delayed due to the lack of knowledge about this uncommon disease and its similarities to other diseases of the myocardium and endocardium. Here we present two cases: an asymptomatic 39-year-old man who was considered to be suffering from dilated cardiomyopathy (DCM) for four years; and an asymptomatic 19-year-old man who was considered to be suffering from hypertrophic cardiomyopathy. In a recent echocardiography study carried out in our echo lab, we recognized the morphological diagnostic criteria of LVNC. Contrast echocardiography, a low-cost, easy, repeatable, real-time, and non-invasive technique with no ionising radiation, shows a high correlation in the diagnosis of LVNC. In echocardiography, the importance of contrast agents is twofold, as they can be considered essential for a reliable differentiation between the compacted and the non-compacted myocardium, while at the same time they allow accurate measurement of the ratio. Heightened clinical suspicion is necessary for the accurate diagnosis and management of diseases.

Non-compaction of the left ventricle (LVNC) is a disorder of endomyocardial morphogenesis that results in multiple trabeculations in the left ventricular myocardium.1 The current literature suggests that LVNC in adults is rare and is associated with a poor prognosis.2-5 However, many studies have reported highly symptomatic cases with a high incidence of ventricular arrhythmia and progressive heart failure. LVNC is a cardiomyopathy characterised anatomically by deep trabeculations in the ventricular wall, which define recesses communicating with the main ventricular chamber. Major clinical correlates include systolic and diastolic dysfunction, associated at times with arrhythmias and embolic events.6

The mechanisms that lead to LVNC are unclear; however, it is widely suggested that the basic morphogenetic abnormality may be an arrest of normal compaction of the loose interwoven mesh of myocardial fibres in the embryo. However, there is little direct evidence, and some authors caution against this interpretation.7

Although echocardiography, in particular contrast echocardiography, has been the diagnostic test of choice for non-compaction, other modalities have been used for the diagnosis, including contrast ventriculography,8,9 computed tomography,9,10 and magnetic resonance imaging (MRI).11-13 MRI provides a good correlation with echo for the localisation and
extent of non-compaction and is useful in cases with poor echocardiographic image quality.\(^{13}\)

**Case presentation**

**Patient 1**

The first case concerned an asymptomatic 39-year-old man who was considered to be suffering from dilated cardiomyopathy (DCM) for four years. The patient's 12-lead electrocardiogram (ECG) was abnormal, with inferior and lateral Q waves, left ventricular hypertrophy, repolarisation changes in leads II, III, AVF, and V\(_4\) to V\(_6\), and non-specific ST elevation in V\(_1\) to V\(_3\).

A chest X-ray showed marked cardiomegaly. The results of routine laboratory work and cardiac enzymes were normal. Electroencephalogram, computerised tomography (CT) brain scan and MRI brain scan were normal. Coronary angiography did not show any occlusive or stenotic lesions.

There were no ST-segment changes or arrhythmia on maximal exercise test. On 24-hour ambulatory ECG recording a number of ventricular extrasystoles were observed. In a recent echocardiography study held in our echo lab, we recognised the morphological diagnostic criteria of LVNC.

**Figures 1 & 2.** Two-dimensional echocardiogram, four-chamber apical view. The colour flow demonstrated communication between intertrabecular spaces and the left ventricular cavity.

**Figures 3 & 4.** Two-dimensional echocardiogram, four-chamber apical view. Contrast echocardiography with intravenous administration of a contrast agent (Sonovue\(^\circledR\)) demonstrated communication between intertrabecular spaces and the left ventricular cavity and shows with great definition the ratio of non-compacted to compacted zone during the end-systolic phase of the cardiac cycle.
Echocardiography showed normal right dimensions according to body surface area. There was increased left ventricular end-diastolic diameter (LVEDD, 60 mm) and impaired left ventricular ejection fraction (LVEF, 45%). There was diastolic dysfunction (E<A) shown by tissue Doppler imaging (TDI). All cardiac valves appeared normal and there were no findings of any coexisting congenital lesion. The left ventricular wall was thickened and had an inhomogeneous appearance with multiple prominent muscular trabeculations present in the left ventricular apex and mid ventricular wall, with deep recesses penetrating the myocardium (Figure 1). These findings were located in the left ventricular inferior and lateral wall. The ratio of the non-compacted to compacted zone during the end-systolic phase of the cardiac cycle was >2.26 (Figure 1). The colour-flow demonstrated communication between intertrabecular spaces and the left ventricular cavity (Figure 2).

Contrast echocardiography with intravenous administration of a contrast agent (Sonovue®) demonstrated communication between intertrabecular spaces and the left ventricular cavity and showed with great definition the ratio of non-compacted to compacted zone during the end-systolic phase of the cardiac cycle (Figures 3 & 4).

Patient 2

The second case concerned an asymptomatic 19-year-old man who has was considered to be suffering from hypertrophic cardiomyopathy. The patient’s 12-lead ECG was normal. Mild cardiomegaly was observed on chest radiography. The results of routine laboratory work and cardiac enzymes were normal. Electroencephalogram, CT brain scan and MRI brain scan were normal. There were no ST-segment changes or arrhythmia on maximal exercise test and 24-hour ambulatory ECG recording.

Echocardiography showed normal right and left dimensions according to body surface area. LVEDD was 47 mm and there was preserved LVEF (50%). Irregularities of diastolic function (E<A) where noted through TDI recording. All cardiac valves appeared normal and there were no findings of any coexisting congenital lesion. Numerous prominent trabeculations in combination with perfused deep intertrabecular spaces in the posterior and lateral left ventricular wall were observed (Figure 5). The ratio of non-compacted to compacted zone during the end-systolic phase of the cardiac cycle was >2.14 (Figure 6). Multiple deep trabeculation recesses communicating with the ventricular cavity were demonstrated by colour Doppler imaging (Figures 6 & 7).

Contrast echocardiography with intravenous administration of a contrast agent (Sonovue®) again demonstrated communication between intertrabecular spaces and the left ventricular cavity and showed with great definition the ratio of non-compacted to compacted zone during the end-systolic phase of the cardiac cycle (Figure 8). Isolated ventricular non-compaction zone segments of the left ventricle were...
identified in the two-dimensional echocardiographic image, using the parasternal long-axis four-chamber view, two-chamber view, and short-axis view.

**Discussion**

Contrast echocardiography has an established role for enhancement of the right heart Doppler signals, the detection of intra-cardiac shunts, and for left ventricular cavity opacification (LVO). LVO is of clinical value for the assessment of cardiac structure and ventricular performance in resting and stress echocardiography. In addition, contrast agents may be used for the enhancement of Doppler signals needed to evaluate diastolic and valvular function. Contrast LVO can improve endocardial border definition, there are theoretical reasons why this may not necessarily translate into more accurate assessment of left ventricular cavity size, volume and function. Attenuation artefacts sometimes obscure the endocardial surface, particularly in the basal segments, and myocardial contrast may confuse the distinction of the border between the blood pool and the endocardium.

CE initially utilised free air in solution but these large, unstable bubbles were not capable of crossing the pulmonary vascular capillary bed, allowing right heart contrast effects only. The first agents capable of left heart contrast after intravenous injection (first generation agents) were air bubbles stabilised by encapsulation (Albunex) or by adherence to microparticles (Leovist). Replacing air with a low solubility fluorocarbon gas stabilises bubbles still further (second generation agents—for example, Optison, SonoVue), greatly increasing the duration of the contrast effect. Third generation agents will use polymer shell and low solubility gas and should produce much more reproducible acoustic properties. Contrast echocardiography improves the diagnostic accuracy of technically suboptimal studies when used in conjunction with harmonic imaging. Intravenous ultrasound contrast agents are indicated for left ventricular opacification and improvement of left ventricular endocardial border delineation in patients with suboptimal acoustic windows. Demonstrated benefits of contrast echocardiography include improvement in the accuracy of left ventricular measurements, regional wall motion assessment, evaluation of non-compaction cardiomyopathy, thrombus detection, Doppler signal enhancement and conjunctive use with stress echocardiography.

Detection of complications of myocardial infarction, such as myocardial rupture and left ventricular pseudoaneurysm formation, has been facilitated by IV contrast injections. Echocardiographic contrast has also been used to enhance the diagnostic capability of transoesophageal echocardiography in suspected ascending aortic dissection by clearly identifying true and false lumina. Space-occupying masses within cardiac chambers, such as thrombi and/or tumours, may also be more easily identified with the
use of intravenously injected intracavitary contrast. Enhanced definition of left and right ventricular morphology may be achieved, which may be particularly valuable in the assessment of asymmetric hypertrophic and right ventricular dysplastic syndromes. Studies have shown the value of contrast echocardiography in the assessment and quantification of myocardial perfusion, and recent clinical trials have suggested a role for contrast perfusion imaging in the stratification of patients with suspected coronary artery disease.

Chin et al described echocardiographic criteria for LVNC. These focus on trabeculae at the left ventricular apex on the parasternal short-axis and apical views, and on left ventricular free-wall thickness at end diastole. LVNC is defined by a ratio of X/Y <0.5, where X is the distance from the epicardial surface to the trough of the trabecular recess, and Y is the distance from the epicardial surface to the peak of the trabeculation. Another proposed standardised method of identifying LVNC is based on:

- absence of coexisting cardiac structural abnormalities;
- numerous, excessively prominent trabeculations and deep intratrabecular recesses;
- recesses supplied by intraventricular blood on colour Doppler; and
- a two-layer structure, with thin compacted layer and a thick non-compacted layer.

End-systolic thickness of the compacted layer and the non-compacted layer of endomyocardium is taken at maximal thickness to calculate the ratio of non-compacted to compacted (N/C) tissue on parasternal short-axis views; LVNC is defined as N/C >2.

The pathogenesis of LVNC has yet to be elucidated, but it has been speculated that this rare congenital disorder results from the arrest of compaction of the myocardium. During normal embryonic growth, endomyocardial trabeculations emerge from the apical region of the primitive ventricles at day 32 of foetal life and involute by day 70 through a process of resorption and remodelling. LVNC is thought to represent a failure of this ‘compaction’ process.

In children, LVNC can occur in Barth syndrome, a rare X-linked multi-system disorder caused by a mutation in the G4.5 gene that encodes the tafazzin family of proteins. However, mutations in this gene in adult LVNC are rare and no mutations in this gene were identified in the first 15 of the 45 patients included in one study. Mutations have been described in adult LVNC in the genes encoding a-dystrobrevin and Cypher/ZASP, integral parts of the complex which links the extracellular matrix of the myocardial cell to the cytoskeleton, and two patients in the current study carried the D117N mutation in Cypher/ZASP. The fact that Cypher/ZASP and a-dystrobrevin are important structural proteins is intriguing, as most published mutations in families with DCM also affect components of the cellular cytoskeleton. Possible genetic loci involved in non-compaction have been described in mice. A mutation in the FKBP12 gene resulted in ventricular septal defects, dilated cardiomyopathy, and non-compaction. Mice lacking the Peg1 gene were found to have alterations in trabeculation similar to those seen in humans with LVNC.

Histologically, isolated non-compaction differs from non-compaction associated with other congenital heart diseases in that the deep intertrabecular recesses communicate with the left ventricular cavity in the former and both the coronary circulation and the left ventricle in the latter. There is no specific histological finding in LVNC, although fibrosis has been described in multiple reports.

Three major clinical manifestations of non-compaction have been described: heart failure, arrhythmias, and embolic events. Findings vary among patients, ranging from asymptomatic left ventricular dysfunction to severe, disabling congestive heart failure. Over two thirds of the patients in the largest series with LVNC had symptomatic heart failure. The most common evidence reported in the literature has been tachypnoea due to low cardiac output. More rarely infants and young children might present cyanosis, syncope, dysmorphic features and failure to thrive.

Depressed ventricular systolic function was noted in 63% of patients reported by Chin et al. Both systolic and diastolic ventricular dysfunction have been described. Restrictive haemodynamics by cardiac catheterisation, as well as an initial presentation of LVNC as a restrictive cardiomyopathy, have been described in children with LVNC.

Diastolic dysfunction in ventricular non-compaction may be related to both abnormal relaxation and restrictive filling caused by numerous prominent trabeculae. The origin of systolic dysfunction in non-compaction is unclear; nonetheless, there is evidence to suggest that subendocardial hypoperfusion and microcirculatory dysfunction play a significant role in ventricular dysfunction and arrhythmogenesis. Chin et al suggested that subendocardial perfusion might be abnormal in LVNC, despite the absence of epicar-
dial coronary artery disease. Under that framework, with numerous trabeculae, subendocardial ischaemia may result from isometric contraction of the endocardium and myocardium within the deep intertrabecular recesses.

Arrhythmias are common in patients with ventricular non-compaction. Atrial fibrillation has been reported in over 25% of adults with LVNC. Ventricular tachyarrhythmias have been reported in as many as 47%. Sudden cardiac death accounted for half of the deaths in the largest series of patients with LVNC. Although ventricular arrhythmias occurred in nearly 40% of patients in the initial description of LVNC by Chin et al, Ichida et al described no cases of ventricular tachycardia or sudden death in the largest series of pediatric patients with LVNC. Paroxysmal supraventricular tachycardia and complete heart block have also been reported in patients with LVNC.

Abnormalities of the resting electrocardiogram (ECG) are found in the majority of patients with LVNC, but findings are non-specific and include left ventricular hypertrophy, repolarisation changes, inverted T waves, ST-segment changes, axis shifts, intraventricular conduction abnormalities, and AV block. Oechslin et al described left bundle branch block in 44% of adult patients with LVNC; however, the reported incidence in children was much lower in another study. Electrocardiographic findings of the Wolff-Parkinson-White syndrome have been described in up to 15% of pediatric patients. Invasive electrophysiological studies in patients with LVNC have not been widely reported. Signal-averaged electrocardiography in 5 children with LVNC showed late potentials in 3 and prolonged QT dispersion in 1. Such findings may help identify individuals at increased risk for ventricular arrhythmias and sudden death.

Treatment for non-compaction of the ventricular myocardium focuses on the 3 major clinical manifestations: heart failure, arrhythmias, and systemic embolic events. Standard medical therapy for systolic and diastolic ventricular dysfunction is warranted. Cardiac transplantation has been used for those with refractory congestive heart failure. Beneficial effects of the β-blocker carvedilol on left ventricular function, mass, and neurohormonal dysfunction in an infant with LVNC have been described. Biventricular pacemakers may have a role in the treatment of LVNC patients with heart failure, reduced left ventricular function, and prolonged intraventricular conduction. Prevention of embolic complications is an additional important issue that should be taken under consideration, and several authors have recommended long-term prophylactic anticoagulation for all patients with ventricular non-compaction, whether or not thrombus has been found. Some have recommended the use of thiamine, coenzyme Q10, riboflavin and carnitine. Because of the familial association described with non-compaction, screening echocardiography of first degree relatives is recommended. Given the high percentage of associated neuromuscular disorders reported in patients with LVNC, neurological and musculoskeletal evaluations are also recommended.

The prognosis in patients with LVNC ranges from a prolonged asymptomatic course to a severe cardiac disability leading to heart transplantation and death. Long-term follow up showed a high incidence of heart transplantation and death. The prognosis is poor and about 50% of adult patients died suddenly. Prognosis is worse in patients with heart failure NYHA class III-IV, left ventricular end-diastolic diameter >60 mm, left bundle branch block and chronic atrial fibrillation. In this group of patients heart transplantation and implantation of an implantable cardioverter-defibrillator may improve long-term survival.

Conclusions

Early diagnosis is considered of high importance for treatment of the disease and prevention of associated complications. Echocardiographic screening is recommended in all first-degree relatives of patients with LVNC in order to identify asymptomatic patients who are at high risk for the serious complications of the disease. Contrast echocardiography should be considered as an extension of the existing echocardiographic examination. Standard laboratory equipment is sufficient to run a contrast echocardiography program. Contrast agents during stress echocardiography may be used to improve the diagnostic accuracy of the test and to study myocardial perfusion. The diagnosis of ischaemia in stress echo relies on the operator’s visual assessment of changes in contractility during stress. Contrast agents must be considered an important tool for improving image quality, especially in patients with an intermediate or poor acoustic window, and their use has been reported to be cost-effective in the few studies designed to this end. Intravenous infusion is easier during stress echocardiography rather than during a resting study,
because the time and cost for the venous line are shared. Under that framework, the cost-effectiveness for the addition of contrast agent is optimal, while patient selection is a critical factor. From the financial perspective (contrast agent and personnel costs, and time allocation) of contrast echocardiography, we are in a position to estimate that without adequate reimbursement there is no incentive to perform the procedure.

The bedside use of contrast echocardiography to assist in adequate image acquisition in the supine, mechanically ventilated, intensive care, or emergency room patient can be helpful. Previously, the clinician could resort only to a transoesophageal echocardiography or nuclear study, but contrast enhanced transthoracic echocardiography imaging can frequently provide the required information without the need for an alternative testing method.

**References**

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