Reviews

Isolated Noncompaction of the Ventricular Myocardium: Contemporary Diagnosis and Management

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Summary: Noncompaction of the ventricular myocardium is a rare form of cardiomyopathy that has been described since the early 1990s. However, noncompaction remains frequently overlooked, in part due to the limited awareness of its unique clinical and imaging characteristics. Contemporary diagnosis has been facilitated by the introduction of specific morphologic criteria by echocardiography and cardiac magnetic resonance. Management issues revolve around the management of heart failure, arrhythmias, and thromboembolic events in order to prevent the significant morbidity and even mortality that has been associated with this entity. Finally, the genetics of noncompaction have been diverse and an issue of clinical importance as it relates to screening of first-degree relatives of affected patients. Two recent cases are presented and many of the contemporary issues in diagnosis and management, based on an extensive review of the literature, are addressed.

Key words: cardiomyopathy, noncompaction, arrhythmias, echocardiography, cardiac magnetic resonance, genetics

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Introduction

Isolated noncompaction of the ventricular myocardium (INVM) is a rare congenital form of cardiomyopathy. The estimated prevalence is 0.014% of patients referred for echocardiography.¹ It is the result of arrest in the normal compaction

process of the ventricular myocardium in the developing fetus. As a result, the left ventricular (LV) wall (and occasionally also the right) is notably thickened with prominent trabeculations and deep intertrabecular recesses that communicate freely with the ventricular cavity. Although initially described in children, several case series have shown this entity to be also present in adults. However, the diagnosis is still frequently delayed, in part due to the limited awareness of the clinical and imaging characteristics of this newly described cardiomyopathy. We present two cases in adults that highlight many of the common clinical features of this syndrome, as well as the important imaging characteristics as assessed by echocardiography and cardiac magnetic resonance (CMR). Issues on management are also presented along with a review of the current literature.

Case Reports

Case No. 1

A 57-year-old Caucasian woman was referred for evaluation of episodes of nonsustained ventricular tachycardia. The patient had a known history of palpitations for several years, with a Holter monitor 6 years prior revealing bursts of atrial tachycardia. Echocardiography at that time was notable for mild depression of LV systolic function (unavailable for review).

The patient was started on a beta blocker and was referred for repeat echocardiography. This revealed dense trabeculations in the apical segment of the left ventricle; deep intertrabecular recesses were noted that appeared to communicate freely with the LV cavity (Fig. 1).

Magnetic resonance imaging revealed isolated noncompaction of the left ventricle involving the apex and extending to the lateral wall and the interventricular septum (Fig. 2).

Given the diagnosis, the associated episodes of nonsustained ventricular tachycardia, and family history of sudden cardiac death, an implantable cardioverter defibrillator (ICD) was placed. The patient continued to receive aspirin and beta blockade. Genetic as well as echocardiographic screening of first-degree relatives was advised.

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FIG. 1 Apical four-chamber view in end diastole (Case No. 1). Prominent trabeculations with deep recesses involve the left ventricular apex and appear to communicate freely with the left ventricular cavity (arrow).

Case No. 2

A 31-year-old man presented with presyncopal episodes and was found to have runs of monomorphic nonsustained ventricular tachycardia on Holter monitor. He apparently had a 10-year history of infrequent presyncopal episodes.

Echocardiography on admission revealed dense trabeculations in the apical segment of the left ventricle; deep intertrabecular recesses were noted that appeared to communicate freely with the LV cavity (Figs. 3 and 4).

FIG. 3 Short-axis view at the distal ventricular level in end diastole (Case No. 2). This reveals significant trabeculations giving a "spongy" appearance to the ventricular myocardium.

FIG. 2 Horizontal long-axis, steady-state free precession cine magnetic resonance image (Case No. 1). Noncompaction of the apical, septal, and lateral regions. The ratio of noncompacted (NC) to compacted (C) segment in the distal septal region is shown and is >2.3 .

Cardiac magnetic resonance was performed (Fig. 5). The spatial resolution was suboptimal due to frequent ventricular ectopy; however, prominent trabeculations were seen in the apical and inferolateral regions.

Subsequent cardiac catheterization revealed elevated filling pressures (Fig. 6) with mild global hypokinesis. The appearance of the left ventricle on ventriculography was not specific (Fig. 7). The coronaries were normal.

The patient underwent implantation of an ICD. Dofetilide was initiated to control the frequent ventricular ectopy. Cardiomyopathy was treated with carvedilol, ramipril, and furo-

FIG. 4 Apical four-chamber view with color flow Doppler in early diastole (Case No. 2). This reveals free communication between the apical deep recesses (arrow) and the main ventricular cavity.

FIG. 5 Horizontal long-axis, steady-state free precession cine magnetic resonance image (Case No. 2). Noncompaction involving the apical region and extending laterally is seen. The spatial resolution of the noncompacted areas is not optimal due to gating issues from frequent ventricular ectopy. The ratio of noncompacted/compacted (NC/C) areas is >2.3 .

semide. Aspirin was initiated and anticoagulation was deferred given the relatively preserved ejection fraction.

Two months later the patient was admitted with ICD discharge due to sustained ventricular tachycardia.

Discussion

Noncompaction of the ventricular myocardium is a rare congenital cardiomyopathy believed to be the result of arrest of normal endomyocardial morphogenesis in the developing fetus.¹ In the literature, noncompaction has been described in isolation—as in our cases—, as well as in combination with other congenital heart abnormalities such as cyanotic heart

disease, right (RV) or LV outflow obstruction, or coronary artery anomalies.¹ It has also been described in association with neuromuscular disorders² such as Becker muscular dystrophy, Emery-Dreifuss muscular dystrophy, myotonic dystrophy, Leber's hereditary optic neuropathy, and Barth syndrome. The left ventricle is always affected; on occasion the right ventricle can also be affected. This cardiomyopathy can be sporadic or familial. Although initially described in children, many patients are now being diagnosed as adults.

Patients can remain asymptomatic or with only minimal symptoms for many years. The classic clinical manifestations include heart failure, arrhythmias, and thromboembolic events.^{1,3-6}

Heart failure is primarily due to systolic dysfunction. Diastolic dysfunction ranging from impaired relaxation to restrictive filling patterns has also been described.^{1,3} Heart failure is the most common reason for hospital admission in these patients. Our patients had invariably some degree of LV systolic dysfunction as well as elevated filling pressures or echocardiographic evidence of diastolic dysfunction. When measured directly during heart catheterization, our patient in Case No. 2 had significantly elevated filling pressures (Fig. 6).

Arrhythmias were the main reason for concern in our patients. Both supraventricular and ventricular tachyarrhythmias have been described in patients with noncompaction.¹⁻⁵ It is hypothesized that due to fibrosis of the trabeculations and subendocardial ischemia, patients with noncompaction are more prone to ventricular arrhythmias.¹ Sudden cardiac death is a significant risk in these patients, with an incidence of 13–18% in some series.^{1,2,4} Case reports have also described association with preexcitation syndromes (Wolff-Parkinson-White).^{5,7}

Systemic thromboembolic complications can be a serious source of morbidity: cerebrovascular accidents, transient ischemic attacks, and mesenteric infarction have been described.⁴ The origin is believed to be from clots forming in the deep intertrabecular recesses; in addition, paroxysmal atrial fibrillation and clot formation due to decreased systolic function are proposed mechanisms.¹ The reported incidence in

FIG. 6 Elevated diastolic filling pressures (end-diastolic of 35 mmHg) (Case No. 2).

FIG. 7 Left ventriculography in the right anterior oblique projection (Case No. 2): Nonspecific appearance of the left ventricle.

adults is as high as 24% over a follow-up period of 6 years.⁸ Chin *et al.*,³ in their original series of eight patients, reported a high thromboembolic risk that appeared to be unrelated to the degree of LV dysfunction. However, a recent, large (n = 62 patients), case-control retrospective study found no difference in the rates of systemic thromboembolism when patients were matched with controls with similar degrees of LV dysfunction.⁹ In addition, a recent review of pathology specimens revealed thrombus formation to be a rare event in noncompacted ventricles.¹⁰ It appears likely that the main risk for cardioembolic events in noncompaction is associated with the severity of the underlying systolic dysfunction and the presence of atrial tachyarrhythmias (reported in as many as 26–29% in large series in adults^{4, 8}) rather than the noncompaction itself. This is important when making decisions regarding long-term anticoagulation.

Echocardiography is the procedure of choice for the diagnosis of this cardiomyopathy. It combines ease of use, portability, and noninvasiveness. Limitations include the inability at times to obtain good windows and especially views of the LV apex due to body habitus, hyperinflated lungs, and so forth. Typical findings include regional increase in wall thickness, mainly affecting the apex and the lateral and inferior wall of the left ventricle. There is a two-layered structure of the myocardial wall; specifically, a thin, compacted epicardial zone and a heavily trabeculated endocardial zone with deep intertrabecular recesses. On Doppler echocardiography, there is blood flow between the ventricular cavity and the recesses. Diagnostic criteria by echocardiography have been proposed¹¹ and include (1) absence of coexisting cardiac abnormalities; (2) a two-layered structure of the LV wall, with the end-systolic ratio of noncompacted to compacted layer >2 (in the short-axis parasternal view); (3) finding this structure predominantly in the apical and mid-ventricular areas; and (4) blood flow directly from the ventricular cavity into the deep intertrabecular recesses as noted by Doppler echocardiography (Fig. 4). Noncompaction of the right ventricle is more difficult to assess by echocardiography. The use of sonicated albumin may be an important adjunct in improving the diagnostic accuracy of echocardiography in more difficult cases.

Cardiac magnetic resonance is emerging as a valuable tool in diagnosing and assessing the extent of ventricular noncompaction.^{12–15} The high spatial resolution allows detailed images of the ventricular myocardium. In addition, it allows assessment of myocardial perfusion, extent of myocardial fibrosis, as well as the presence of ventricular thrombus.⁶ Recently, specific morphologic criteria were proposed for the diagnosis of noncompaction by CMR imaging.¹⁵ Specifically, an end-diastolic ratio between noncompacted to compacted segment >2.3 appears to distinguish pathologic noncompaction reliably from the prominent trabeculations seen occasionally in normal individuals, trained athletes, patients with LV hypertrophy (due to hypertension or valvular heart disease), patients with hypertrophic cardiomyopathy, and patients with dilated cardiomyopathy. The role of CMR in the diagnosis of noncompaction is critical when echocardiographic windows are limited or when echocardiography cannot distinguish reliably between noncompaction and other cardiac pathology such as apical hypertrophy, endomyocardial fibroelastosis, metastatic disease, or apical thrombus.¹ Otherwise, a good echocardiographic study can accurately diagnose noncompaction based on the aforementioned criteria⁸ without the need for CMR.

Left heart catheterization is not considered a first line diagnostic modality for identifying noncompaction. Rather, it provides supplemental evidence in the patient already suspected of having this entity, allows direct measurement of LV filling pressures, and helps exclude coronary artery disease as the cause of LV dysfunction and arrhythmias.

Treatment decisions in patients with noncompaction focus on all three of the major clinical manifestations. Heart failure management should be according to the established guidelines for systolic dysfunction. Arrhythmias should be monitored at least annually by ambulatory electrocardiography monitor. Given the risk for ventricular arrhythmias and sudden cardiac death, the use of an ICD should be considered, especially if there is a strong family history of sudden death, high-grade ventricular ectopy on Holter monitoring, or symptoms suggestive of paroxysmal tachyarrhythmias. Finally, all patients should at a minimum be treated with antiplatelet therapy. Some authors actually suggest anticoagulation for all patients with

TABLE 1 Identified genes or chromosomal loci

Gene	Location	Protein	Phenotypic expression
TAZ (G4.5)	Xq28	Tafazzin	X-linked recessive; neonatal onset; isolated noncompaction; association with Barth syndrome, myotubular myopathy, and other neuromuscular disorders ¹⁶
Cypher/Zasp	10q22.2-23.3	ZASP (Z line alternatively spliced PDZ-motif protein)	Autosomal dominant; dilated cardiomyopathy or isolated noncompaction ¹⁹
CSX	5q34	NKX 2.5	Autosomal dominant. Noncompaction and other congenital heart disease (tetralogy, atrial septal defects, second-degree atrioventricular block) ²⁰
DTNA	18q12.1-q12.2	α -dystrobrevin	Autosomal dominant. Nonisolated ventricular noncompaction ¹⁶
MLP/SOX6	11p15	?	Autosomal dominant. Isolated noncompaction. Adult patients ¹⁸

noncompaction,⁴ but based on recent studies^{9,10} this may only be necessary for those with significant systolic dysfunction, paroxysmal atrial arrhythmias, or a history of embolic events.

The prognosis for patients with noncompaction appears unfavorable in the reviewed case series.^{1,3,4} Progressive congestive heart failure, arrhythmias, and even sudden death are the major causes for morbidity and mortality. Poor prognostic markers include the development of atrial fibrillation, bundle-branch block, dilated LV end-diastolic diameter, and New York Heart Association (NYHA) class III–IV.⁴ Early consideration for transplant should be undertaken in these patients.

The studies looking into the genetics of ventricular noncompaction suggest significant heterogeneity in the genetic substrate for this disorder. According to one report, up to 50% of infantile³ and up to 18% of adult cases⁴ of noncompaction are familial, with the remainder being sporadic. Both X-linked as well as autosomal transmission has been observed. In the former, mutations of the TAZ (G4.5) gene located in the Xq28 region cause noncompaction associated with other neuromuscular disorders and affect male offspring (X-linked recessive).¹⁶ The majority of cases causing familial clustering in adults are not X-linked but rather transmitted in an autosomal dominant manner.¹⁷ Several genes or chromosomal loci have been identified (see Table 1). Of these, mutations to the 11p15 locus¹⁸ (unidentified gene) and to the Cypher/ZASP¹⁹ lead to isolated noncompaction, whereas mutations in the CSX²⁰ or the DTNA¹⁶ genes usually cause other congenital heart diseases in addition to noncompaction. It is difficult to make specific recommendations for genetic screening in patients identified as having noncompaction. The prognostic significance of identifying any of the aforementioned genetic mutations is not clear. A detailed family history (focusing on sudden cardiac death, cardiomyopathies, heart failure, and arrhythmias as well as congenital heart disease and neuromuscular disorders) is mandatory in all patients. Further genetic testing would be of interest in those with a positive family history. Echocardiographic imaging of first-degree relatives is well justified.

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